DRAFT
TOXICOLOGICAL PROFILE FOR PYRETHRINS AND PYRETHROIDS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

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<u>Background Information</u>

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on October 21, 1999 (64 FR 56792). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); and November 17, 1997 (62 FR 61332). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Jeffrey P. Koplan, M.D., M.P.H.
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Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by *type of health effect* (death, systemic, immunologic, reproductive), by *route of exposure*, and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.8 Biomarkers of Exposure and Effect
Section 3.11 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 *Fax:* (404) 498-0057
E-mail: atsdric@cdc.gov *Internet:* http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

*The National Institute of Environmental Health Sciences (*NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for pyrethrins and pyrethroids. The panel consisted of the following members:

1. Val Richard Beasley, D.V.M., Ph.D., Professor of Veterinary, Wildlife, and Ecological Toxicology, Director, Envirovet Program in Wildlife and Ecosystem Health, University of Illinois at Urbana-Champaign, College of Veterinary Medicine, Urbana, Illinois;

2. Syed Ghiasuddin, Ph.D., State Environmental Toxicologist and Section Chief, Indiana Department of Environmental Management, Indianapolis, Indiana; and

3. William Valentine, D.V.M., Ph.D., Associate Professor of Pathology, Vanderbilt University Medical Center, Nashville, Tennessee.

These experts collectively have knowledge of pyrethrins' and pyrethroids' physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about pyrethrins and pyrethroids and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Pyrethrins have been found in at least 5 of the 1,585 current or former NPL sites and permethrin has been found in at least 2 of the 1,585 current or former NPL sites. No other pyrethroids were detected at the NPL sites. However, the total number of NPL sites evaluated for these substances are not known. As more sites are evaluated, the sites at which pyrethrins and pyrethroids are found may increase. This information is important because exposure to these substances may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to pyrethrins or pyrethroids, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with them. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT ARE PYRETHRINS AND PYRETHROIDS?

Pyrethrum is a naturally occurring mixture of chemicals found in certain chrysanthemum flowers. Pyrethrum was first recognized as having insecticidal properties around 1800 in Asia and was used to kill various insects such as fleas, mosquitos, and ticks. Six individual chemicals have active insecticidal properties in the pyrethrum extract, and these compounds are called pyrethrins. Pyrethrum looks like a tan colored dust as ground flowers or a syrupy liquid as the crude extract. Pyrethrins are only slightly soluble in water, but they are soluble in organic solvents like alcohol, chlorinated hydrocarbons, and kerosene. The pyrethrins are often used in household insecticides and products to control insects on pets or livestock. The pyrethrins break down quickly in the environment, especially when exposed to natural sunlight.

Pyrethroids are manufactured chemicals that are very similar in structure to the pyrethrins, but are often more toxic to insects as well as to mammals, and last longer in the environment than the pyrethrins. More than 1,000 synthetic pyrethroids have been developed, but less than a dozen of them are currently used in the United States. Pyrethrins and pyrethroids are often combined commercially with other chemicals called synergists, which enhance the insecticidal activity of the pyrethrins and pyrethroids. The synergists prevent some enzymes from breaking down the pyrethrins and pyrethroids, thus increasing their toxicity.

Most commercial pyrethroids are not one single molecule; rather, they are several molecules with the same chemical formula that have their atoms joined together in the same sequence, but have a different arrangement of the atoms in space. Such compounds are called stereoisomers. If the stereoisomers are not mirror images of one another, they are called diastereomers and have different physical properties like boiling point, melting point, and solubility. If they are nonsuperimposable mirror images of each other, they are called enantiomers and properties like boiling point, melting point, and solubility are identical. However, both diastereomers and enantiomers can have different insecticidal properties and different toxicities. Some pyrethroids are composed of as many as eight different stereoisomers.

1.2 WHAT HAPPENS TO PYRETHRINS AND PYRETHROIDS WHEN THEY ENTER THE ENVIRONMENT?

Pyrethrins and pyrethroids are primarily released to air because of their use as insecticides. Sometimes they are sprayed on crops from planes and helicopters or sprayed from the ground by trucks, tractors or hand held applicators. They are also used to control flying insects like mosquitos and flies on livestock and pets. These compounds are also in aerosol bombs and sprays that can be used indoors. Pyrethrins can be released naturally from chrysanthemum flowers, but these releases are small compared with the amounts used as commercial insecticides. Manufacturing facilities that produce these compounds can also release them to the environment during the production process.

In air, all six of the pyrethrins and many of the pyrethroids are broken down or degraded rapidly by sunlight or other compounds found in the atmosphere. Often, they last only 1 or 2 days before being degraded. Rain and snow help remove the pyrethroids from air that are not rapidly degraded. Since many of these compounds are extremely toxic to fish, usually they are not sprayed directly onto water, but they can enter lakes, ponds, rivers, and streams from rainfall or runoff from agricultural fields. These compounds bind strongly to dirt and usually are not very mobile in soil. Pyrethrins and pyrethroids are not easily taken up by the roots of plants and vegetation because they are strongly bound to the soil; however, they are often sprayed directly onto crops and plants so they may be found on leaves, fruits and vegetables. Because these compounds adsorb so strongly to soil, pyrethrins and pyrethroids usually do not leach into groundwater and do not contaminate drinking water supplies. These compounds are eventually degraded by the microorganisms in soil and water. They can also be degraded by sunlight at the surfaces of water, soil, or plants. However, some of the more recently developed pyrethroids can persist in the environment for a few months before they are degraded.

For more information about the fate and movement of pyrethrins and pyrethroids in the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO PYRETHRINS AND PYRETHROIDS?

You can be exposed to pyrethrins and pyrethroids in several ways. Eating foods that are contaminated with these compounds is the most likely way. You can also breathe in air that contains these compounds. This is especially possible soon after the insecticide has been sprayed. After spraying, these compounds can also come in contact with your skin and you can be exposed by dermal contact. These compounds are contained in many household insecticides, pet sprays, and shampoos. Some pyrethroids are also used as lice treatments that are applied directly to the head and as mosquito repellents that can be applied to your clothes. The use of these products can lead to exposure.

The average daily intake of permethrin (the most frequently used pyrethroid in the United States) for a 70 kilogram adult male is estimated as about 3.2 micrograms per day (1 microgram equals 1/1,000,000 of a gram).

1.4 HOW CAN PYRETHRINS AND PYRETHROIDS ENTER AND LEAVE MY BODY?

Pyrethrins and pyrethroids usually enter the body when people eat foods contaminated by these chemicals. They may also enter your body by breathing air that contains these compounds or through dermal exposure when you use commercially available insecticides that contain pyrethrins and pyrethroids. These chemicals are absorbed by the body when you eat contaminated foods and breathe contaminated air, but they are not as easily absorbed through the skin when you touch contaminated soil, vegetation, or insecticides containing these compounds. Pyrethrins and pyrethroids can enter your body if you swallow drinking water contaminated with these compounds, but since pyrethrins and pyrethroids are rarely found in drinking water, this will be a minor exposure route.

Pyrethrins and pyrethroids that enter the body leave quickly, mainly in the urine, but also in feces and breath. These compounds are also quickly broken down by the body into other chemicals called metabolites. The concentration of these chemicals in the urine increases as the amount of the exposure goes up. If exposure levels are very high or if exposure occurs over a long time, then pyrethrins and pyrethroids can build up in fatty tissue and remain in the body for a little longer. Certain types of pyrethroids can also be retained for longer periods of time in the skin and hair.

Chapter 3 contains more information on how pyrethrins and pyrethroids enter and leave the human body.

1.5 HOW CAN PYRETHRINS AND PYRETHROIDS AFFECT MY HEALTH?

Pyrethrins and pyrethroids interfere with the way that the nerves and brain function. If you get a large amount of pyrethrins or pyrethroids on your skin, you may get feelings of numbness, itching, burning, stinging, tingling, or warmth that could last for a few hours. You are not likely to be exposed to amounts of pyrethrins or pyrethroids by breathing air, eating food, or touching anything that would cause enough pyrethrins or pyrethroids to enter your body and cause other problems. But if very large amounts of these chemicals were to enter your body, you might experience dizziness, headache, and nausea that might last for several hours. Larger amounts might cause muscle twitching, reduced energy, and changes in awareness. Even larger amounts could cause convulsions and loss of consciousness that could last for several days. There is no evidence that pyrethrins or pyrethroids cause birth defects in humans or affect the ability of humans to produce children. There is no proof that pyrethrins or pyrethroids cause cancer in people.

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Animal studies show effects of pyrethrins and pyrethroids similar to those seen in people exposed to very high amounts of these chemicals. In addition, exposure to pyrethrins or pyrethroids might affect the ability of some animals to reproduce. Pyrethrins and pyrethroids to not appear to cause cancer in animals.

1.6 HOW CAN PYRETHRINS AND PYRETHROIDS AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

Children exposed to large amounts of pyrethrins or pyrethroids would be expected to be affected in the same manner as adults. If children were to get a large amount of pyrethrins or pyrethroids on their skin, they might get feelings of numbness, itching, burning, tingling, or warmth that could last for a few hours. If very large amounts of these chemicals were to enter a child's body, the child might experience dizziness, headache, and nausea that might last for several hours. Even larger amounts could cause muscle twitches, tremors, convulsions, and loss of consciousness that could last up to several days.

There is no evidence in humans that pyrethrins or pyrethroids cause birth defects. Some young animals showed signs of possible damage to the body's defense system that fights infection after their mothers were exposed to pyrethroids while their babies were developing in the womb. Animal studies show that some adults might show changed behavior if they had been exposed to pyrethroids soon after birth when the brain was rapidly developing.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO PYRETHRINS AND PYRETHROIDS?

If your doctor finds that you have been exposed to significant amounts of pyrethrins or pyrethroids, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

Pyrethrins and pyrethroids are effective insecticides that are often used in household sprays, aerosol bombs, insect repellents, pet shampoos, and lice treatments. Using products containing these compounds will expose you to these chemicals. If you decide to use these products, carefully follow the instructions on how to apply them properly and how long to wait before re-entering the treated area. Do not apply more than the recommended amount. Pesticides and household chemicals should be stored out of reach of young children to prevent accidental poisoning. Always store pesticides in their original labeled containers; never store pesticides in containers that young children would find attractive, such as old soda bottles. If you feel sick after a pesticide has been used in your home, see a doctor or call the local poison control center. Keep your poison control center's number next to the phone. If a close neighbor or someone living nearby is applying pyrethrins or pyrethroids, you may want to remain indoors with your children and pets. Certain pyrethroids, such as permethrin, phenothrin, and resmethrin, are sprayed to control mosquitos during the spring and summer. Remaining indoors and closing your windows while your neighborhood is being sprayed will lessen your exposure.

Since these compounds frequently are used on crops, they are often detected in fruits and vegetables. Make sure you wash fruits and vegetables thoroughly before eating them. Trim the fat from meat and poultry because pesticides often concentrate in fat. These compounds are often detected in soils, especially in agricultural areas. Some children eat a lot of dirt. You should discourage your children from eating dirt. Make sure they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or any other hand-to-mouth activity.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO PYRETHRINS OR PYRETHROIDS?

Methods exist that can detect pyrethrins and pyrethroids in blood and urine. Because these compounds are broken down in the body quickly, there are also ways to measure the metabolites of these chemicals in human blood and urine. These methods usually are not available in a doctor's office because special equipment is required. However, a sample taken in a doctor's office can be shipped to a special medical laboratory, if necessary. Because pyrethrins and pyrethroids break down in the body rapidly, these methods are useful only if exposure has occurred within the last few days. At this time, these methods can tell only if you have been exposed to pyrethrins or pyrethroids and cannot tell if you will have any adverse health effects. Methods also exist that can measure the concentration of pyrethrins and pyrethroids in air, water, soil, and foods.

Chapter 7 contains more information regarding the measurement of pyrethrins and pyrethroids in humans and environmental samples.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for pyrethrins and pyrethroids include the following:

The World Health Organization (WHO) has recommended that the level of permethrin in drinking water not exceed 20 micrograms per liter (μg/L). OSHA regulates the level of pyrethrins in workplace air. The occupational exposure limits for an 8-hour workday, 40-hour workweek are 5 mg per cubic meter (mg/m^3). The EPA has recommended daily oral exposure limits for 10 different pyrethroids. These limits range from 0.005 to 0.05 mg/kg/day.

For more information on regulations and guidelines, see Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)
Fax: 1-404-498-0057

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PYRETHRINS AND PYRETHROIDS IN THE UNITED STATES

Pyrethrum is the natural extract that occurs in the flowers of *Chrysanthemum cinerariaefolium* and *Chrysanthemum cineum*. Pyrethrum has long been recognized as possessing insecticidal properties; over the years, first the chemical extracts of pyrethrum, and then more recently, the specific synthetic chemical analogs have been produced. The six active insecticidal compounds of pyrethrum are called pyrethrins. The six individual pyrethrins are pyrethrin I, pyrethrin II, cinerin I, cinerin II, jasmolin I, and jasmolin II. The pyrethroids are synthetic analogs and derivatives of the original pyrethrins and represent a diverse group of over 1,000 powerful insecticides. Although they are based on the chemical structure and biological activity of the pyrethrins, the development of synthetic pyrethroids has involved extensive chemical modifications that make these compounds more toxic and less degradable in the environment. A list of the pyrethrins and some of the more common pyrethroids are shown in Table 2-1. While many pyrethroids have been developed, only about a dozen or so are frequently used in the United States. The individual pyrethroids are typically grouped into two general classes, called Type I and Type II, based on a combination of toxicological and physical properties, which is further described in Chapters 3 and 4. Also, the individual pyrethroid substances, due to a complex chemical structure, are often composed of two, four, or eight isomers, and their commercially manufactured products routinely contain a mixture of these various isomers. Thus, the production of individual pyrethroids with slightly varying isomeric ratios can often be the reason for the differences in the reported toxicities of the same compound. See Chapter 4 for the structures and explanation of the isomerism, as well as more information on the chemical and physical properties of the pyrethrins and pyrethroids.

Both groups, the pyrethrins and the pyrethroids, are very important insecticides because of their rapid paralysis of flying insects, relatively low mammalian toxicity, and rapid rate of degradation in the environment. They are typically used as insecticides for both home and commercial use. Also, the pyrethrins and pyrethroids are often formulated with compounds such as piperonyl butoxide, piperonyl sulfoxide, and sesamex, which act as synergists to increase the effectiveness of the insecticide. Currently, the products containing small amounts of pyrethroids for uses around the home are still classified as general use pesticides; however, emulsified or granular concentrate formulations that are applied to fields were classified as restricted use pesticides by EPA in 1995.

Table 2-1. Pyrethrins and Pyrethroids Discussed in the Profile[a]

Pyrethrins	Type I pyrethroids	Type II pyrethroids
Constituents of natural pyrethrum extract	Derivatives of pyrethrins that do not include a cyano group and may elicit tremors	Derivatives of pyrethrins that include a cyano group and may elicit sinuous writhing (choreoathetosis) and salivation
Pyrethrin I	Allethrin	Cyfluthrin
Pyrethrin II	Bifenthrin	Cyhalothrin
Cinerin I	Permethrin	Cypermethrin
Cinerin II	Phenothrin(Bio)	Deltamethrin
Jasmolin I	Resmethrin	Fenvalerate
Jasmolin II	Tefluthrin	Fenpropathrin
	Tetramethrin	Flucythrinate
		Flumethrin
		Fluvalinate
		Tralomethrin

[a]Type I and Type II pyrethroids are described in more detail in Section 3.5.2, Mechanisms of Toxicity

Pyrethrins and pyrethroids are released to the environment due to their use as insecticides. They can be applied to crops from aerial and ground based sprayers or applied indoors from commercially available sprays or aerosol bombs. These compounds are readily degraded in the atmosphere by natural sunlight and usually do not persist for more than several days to a few weeks. Certain pyrethroids such as permethrin and cyhalothrin, where the isobutenyl group attached to the cyclopropane moiety has been altered, are slightly more stable to sunlight than other pyrethroids. Air concentrations are usually in the $\mu g/m^3$ range (both indoors and outdoors) after spraying, but diminish over time as these compounds are degraded or removed by wet and dry deposition. In soils, pyrethrins and pyrethroids are not very mobile and usually do not leach into groundwater. These compounds are biodegraded in soil and water and can also undergo hydrolysis under alkaline conditions. Since these compounds adsorb strongly to soils, they are not taken up substantially by the roots of vascular plants. These compounds bioconcentrate in aquatic organisms and are extremely toxic to fish.

The general population is primarily exposed to pyrethrins and pyrethroids from the ingestion of foods, particularly vegetables and fruits. Exposure due to inhalation of ambient air is also possible after these compounds have been used. Pyrethrins and pyrethroids are also employed in a variety of pet shampoos, lice treatments, household insecticide sprays, and aerosol bombs that can be used in or around the home, and the use of these products can lead to both dermal and inhalation exposure. Occupational exposure to agricultural workers who apply these compounds onto crops can be substantial, with dermal exposure considered the most important pathway (see Section 6.5).

The average daily intake (AVDI) of permethrin for eight different age/sex groups has been estimated from market basket surveys conducted by the Food and Drug Administration (FDA). Based upon market basket surveys conducted from 1986 to 1991, the AVDI of permethrin ranges from about 36 to 71 ng/kg/day (see Table 6-4). Since permethrin is the most frequently used pyrethroid in the United States, the data from these surveys may represent a reasonable first approximation for the average total intake of all the pyrethroids.

2.2 SUMMARY OF HEALTH EFFECTS

Pyrethrins and pyrethroids are used extensively as effective insecticides, but pose relatively little hazard to mammals (including humans) by natural routes of exposure at levels likely to be encountered in the environment or resulting from the normal use of pyrethrin- or pyrethroid-containing substances. Signs and symptoms of acute toxicity vary according to the type of pyrethroid to which one may be exposed. However, almost all systemic effects are related to the action of pyrethrins and pyrethroids on the nervous system. These chemicals exert their profound effect by prolonging the open phase of the sodium channel gates when a nerve cell is excited. In rodents, effects such as tremors are induced if the open state is prolonged for brief periods; effects such as sinuous writhing (choreoathetosis) and salivation occur if the open state is prolonged for longer periods. Neurological signs typically result from acute toxicity. Low-level chronic exposures to pyrethrins and pyrethroids usually do not cause neurological signs in mammals, largely due to rapid metabolism and elimination. Available animal data do not indicate that pyrethrins or pyrethroids significantly affect end points other than the nervous system, although changes in liver weight and metabolism of chemicals have sometimes been used as an index of adverse effect levels for pyrethroids. A few recent animal studies indicate the potential for adverse neurodevelopmental, reproductive, and immunological effects at exposure levels below those expected to result in overt signs of neurotoxicity. Available data do not indicate that pyrethrins or pyrethroids should be considered a carcinogenic concern to humans. No human data are available regarding the potential for pyrethroids to cross the placental barrier and enter a developing fetus. Limited animal data indicate that transfer of pyrethroids across the placenta to the fetus may occur, which may result in persistent effects on neurotransmitters later in life. Although pyrethroids have not been identified in human breast milk, very low levels of pyrethroids (<1% of an orally administered dose) are excreted into milk of lactating animals.

Neurological Effects. Pyrethrins and pyrethroids act principally on the sodium channels of nerve cells in exerting their toxic effects. Two different types of pyrethroids are recognized, based on differences in basic structure (the presence or absence of a cyano group in the alpha position) and the symptoms of poisoning in laboratory rodents. Type I pyrethroids do not include a cyano group; their effects typically include rapid onset of aggressive behavior and increased sensitivity to external stimuli, followed by fine tremor, prostration with coarse whole body tremor, elevated body temperature, coma, and death. The term T-syndrome (from tremor) has been applied to Type I responses. Clinical signs of neurotoxicity in animals exposed to pyrethrins are similar to those of Type I pyrethroids. Type II pyrethroids include a cyano group; their effects are usually characterized by pawing and burrowing behavior, followed by profuse salivation, increased startle response, abnormal hind limb movements, and coarse whole body tremors that progress to sinuous writhing (choreoathetosis). Clonic seizures may be observed prior to death. Body temperature usually is not increased, but may decrease. The term CS-syndrome (from choreoathetosis and salivation) has been applied to Type II responses. In general, the distinction between Type I and Type II pyrethroids is clear. However, two of the cyano-pyrethroids, fenpropathrin and cyphenothrin, have been shown to trigger responses intermediate to those of T- and CS-syndrome, characterized by both tremors and salivation. These neurological responses to pyrethroid poisoning are typically of acute duration. There is no evidence to indicate that long-term low-level exposure of adults to pyrethroids might result in them experiencing more severe neurological effects.

Whereas distinctive signs of these neurotoxic symptoms (T- and CS-syndrome) occur in humans diagnosed with mild to severe pyrethroid poisoning, levels high enough to trigger these symptoms are not likely to occur under most exposure scenarios. Occupational exposure to pyrethroids (particularly Type II pyrethroids containing the cyano group) has frequently led to paresthesia (abnormal cutaneous sensations such as tingling, burning, stinging, numbness, and itching) among individuals exposed via unprotected areas of the skin. This effect is often observed at exposure levels far below those in which other clinical signs of neurotoxicity might be expected to occur. Some animal studies indicate that exposure to pyrethroids may result in other less overt signs of neurotoxicity, such as changes in startle and avoidance responses, altered levels of spontaneous motor activity, and changes in operant conditioned responses, which may occur at levels below those eliciting typical T- or CS-syndrome. Some of these effects can be particularly observed in adult animals that had been exposed to pyrethroids during critical stages of neonatal neurological development.

Developmental Effects. Standard developmental studies have not elucidated typical signs of developmental toxicity in animals exposed to pyrethrins or pyrethroids. However, when exposed to pyrethroids during critical stages of neonatal neurological development, mice later exhibited persistently increased spontaneous motor activity. *In utero* exposure of rats resulted in cellular changes indicative of compromised immunological function.

Reproductive Effects. Standard reproductive toxicity studies, including some that were performed for three successive generations, did not indicate that pyrethrins or pyrethroids might be of particular concern to reproductive success. However, a few recent studies have indicated that relatively low-level, intermediate-duration oral exposure of adult male laboratory animals to some Type II pyrethroids may result in damage to reproductive organs, abnormal sperm characteristics, reduced plasma testosterone levels, and reduced fertility.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

No inhalation MRLs were derived for pyrethrins or pyrethroids for inhalation exposure since adequate data were not available by this route of exposure.

Oral MRLs

No oral MRLs were derived for pyrethrins since adequate data were not available. Two oral MRLs were derived for specific pyrethroids.

- An MRL of 0.0007 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to bioallethrin (Type I pyrethroid).

This MRL is based on a LOAEL of 0.21 mg/kg/day for neurodevelopmental effects in mice. An uncertainty factor of 300 was used (10 for use of a LOAEL, 10 for animal to human extrapolation, and 3 to account for intrahuman variation).

- An MRL of 0.002 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to deltamethrin (Type II pyrethroid).

This MRL is based on a LOAEL of 0.7 mg/kg/day for neurodevelopmental effects in mice. An uncertainty factor of 300 was used (10 for use of a LOAEL, 10 for animal to human extrapolation, and 3 to account for intrahuman variation).

The most significant finding in the available literature was the presence of altered motor behavior in adult mice treated with bioallethrin (Type I pyrethroid) or deltamethrin (Type II pyrethroid) neonatally. Groups of 10-day-old male NMRI mice were treated by gavage with 0 (vehicle control), 0.7 mg bioallethrin/kg, or 0.7 mg deltamethrin/kg in a fat emulsion vehicle by gavage for 7 consecutive days. Following treatment cessation, 17-day-old mice were tested for spontaneous activity (locomotion). At the age of 4 months, the mice were subjected to behavioral tests of spontaneous activity (locomotion, rearing, and total activity). Tests were conducted for 1 hour, and scores were summed for three 20-minute periods. Locomotor activity in the 17-day-old mice was not significantly different from that in controls. However, when tested at 4 months of age, bioallethrin-treated mice showed significantly more locomotion throughout the 1-hour test period and significantly increased rearing and total activity during the last 40 minutes of testing, relative to controls. Deltamethrin-treated mice exhibited significantly increased locomotion and total activity during the last 20 minutes of the test period. This was interpreted as disruption of a simple, nonassociative learning process, (i.e., habituation), or a retardation in adjustment to a new environment. Receptor assays, performed 1–2 weeks following behavioral testing at 4 months of age, revealed a significant decrease in muscarinic acetylcholine (MACh) receptor density in the cerebral cortex of bioallethrin-treated mice and a trend toward a decrease in deltamethrin-treated mice. No significant treatment-related changes in this parameter were seen in two other brain regions, hippocampus and striatum. A similarly designed dose-response study of bioallethrin was performed using oral doses of 0, 0.21, 0.42, 0.7, and 42 mg bioallethrin/kg. When behaviorally tested at 4 months of age, mice treated with bioallethrin doses of 0.21–0.7 mg/kg/day exhibited significantly increased spontaneous locomotor activity, relative to controls. Analysis of MACh receptor density revealed dose-related increased density in 17-day-old mice and dose-related decreased density in 4-month-old mice. In contrast to the findings in the 0.21–0.7 mg/kg dose groups, mice receiving 42 mg bioallethrin/kg daily exhibited significant decreases in locomotion and total activity counts and no significant differences in MACh receptor density. Underlying mechanisms responsible for the differences observed in low-dose groups (0.21–0.7 mg/kg) and mice in the 42 mg/kg dose group, a level approaching that which would be expected to result in overt clinical signs of neurotoxicity, could not be explained.

From these studies, it is apparent that oral exposure of neonatal mice to pyrethroid levels below those resulting in overt signs of acute neurotoxicity may cause changes in receptor densities within the brain that can be observed shortly following treatment, and also following maturation. Neonatal exposure can also cause changes in behavioral patterns that are first apparent in adulthood. However, a causal relationship between changes in muscarinic cholinergic receptor populations in the cerebral cortex and increased spontaneous motor activity has not been established. The pyrethroid-induced increases in spontaneous motor activity at doses of 0.21 and 0.7 mg/kg (for bioallethrin and deltamethrin, respectively) are considered less serious LOAELs. An uncertainty factor of 3 instead of 10 was used to account for human variability in the derivation of acute oral MRLs for both bioallethrin and deltamethrin, since the neonatal rat (10 days old) is a sensitive subject. Levels resulting in no-observed-adverse-effects were not identified in these studies and the sensitivity of human neonates is unknown.

MRLs for intermediate- and chronic-duration oral exposures to pyrethroids were not derived because animal studies in which health effects were assessed following oral administration of pyrethroids for intermediate (15–364 days) or chronic (365 days or more) durations identified LOAELs that were higher than the LOAELs of 0.21 and 0.7 mg/kg/day for neurodevelopmental effects in mice following acute-duration oral exposure to bioallethrin and deltamethrin, respectively.

The acute oral MRLs derived for bioallethrin and deltamethrin are specific to these two pyrethroids. As additional information becomes available regarding adverse effects associated with low-level exposure to other pyrethroids, such information could be used to develop MRLs specific to these pyrethroids as well. Also, the acute oral LD_{50} values are generally lower in Type II pyrethroids than in Type I pyrethroids indicating a greater degree of toxicity for Type II pyrethroids. However, this is not reflected in the two ATSDR derived MRLs, where the Type I pyrethroid (bioallethrin) has a slightly lower MRL than the Type II pyrethroid (deltamethrin). This suggests that further testing should be done to evaluate whether different stages of development, that is, organismal age, could account for such differences in relative toxicity.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of pyrethrins and pyrethroids. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for pyrethroids. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

Pyrethrum, the natural extract of the flowers of *Chrysanthemum cinerariaefolium* and *Chrysanthemum cocineum*, contains six active insecticidal compounds called pyrethrins. Pyrethroids are synthetic analogs and derivatives of pyrethrins and represent a diverse group of over 1,000 powerful insecticides (Mueller-Beilschmidt 1990). Although they are based on the chemical structure and biological activity of the pyrethrins, the development of synthetic pyrethroids has involved extensive chemical modifications that make these compounds more toxic and less degradable in the environment. The pyrethrins and some of the more common pyrethroids are listed in Table 2-1. Pyrethrins and pyrethroids pose relatively little hazard to mammals (including humans) by common routes of exposure at levels likely to be encountered in the environment or resulting from the normal use of pyrethrin- or pyrethroid-containing substances.

Two different types of pyrethroids are recognized, based on differences in basic structure (the presence or absence of a cyano group) and the symptoms of poisoning in laboratory rodents (Coats 1990; Verschoyle and Aldridge 1980). In general, Type I pyrethroids do not include a cyano group, and clinical signs of Type I pyrethroid-induced toxicity include whole body tremors. Type II pyrethroids include a cyano group and are characterized by their elicitation of salivation and sinuous writhing (choreoathetosis).

Toxicity among the various pyrethroids varies greatly, as is evidenced by the wide range in LD_{50} values (concentrations or doses that result in 50% mortality in exposed laboratory animals). These differences are dependent on a number of factors including specific pyrethroid, ratios of stereo and optical isomers within a given pyrethroid formulation, and vehicle. Acute oral LD_{50} values are generally lower in Type II than Type I pyrethroids, indicating a greater degree of toxicity for Type II pyrethroids. In the case of tetramethrin, like all other Type I pyrethroids, isomers of the 1R conformation are considerably more toxic than those of the 1S conformation. The 1S isomer can also inhibit toxicity by competitive inhibition at a number of stereospecific pyrethroid binding sites, thus preventing binding of the more toxic 1R isomer (Narahashi 1986). Furthermore, it has been observed that the cis isomers possess greater mammalian toxicity than the trans isomers. For Type II pyrethroids, the S conformation at the alpha carbon adjacent to the cyano group is considerably more toxic than the R conformation. Consult Chapter 4 for additional information regarding the structural properties of Type I and Type II pyrethroids.

Neurological signs are typically the result of acute toxicity and do not appear to be significantly amplified following repeated low-level exposures. This may be a result of rapid metabolism and elimination of pyrethrins and pyrethroids by mammals. Available animal data indicate that the nervous system is the primary target of pyrethrin- or pyrethroid-induced toxicity. However, changes in liver weight and liver metabolism of chemicals have sometimes been used as an index of adverse effect levels for pyrethroids. In addition, a few recent studies indicate the potential for adverse neurodevelopmental, reproductive, and immunological effects at exposure levels below those expected to result in overt signs of neurotoxicity. Available data do not indicate that pyrethrins or pyrethroids may be a carcinogenic concern to humans.

Based on the wide range of differences in levels of animal toxicity to the various pyrethroids, factors related to chemical properties and exposure scenarios of a given pyrethroid must be taken into account when assessing the risk related to exposure of humans to pyrethroids. The acute oral Minimum Risk Levels (MRLs) derived for bioallethrin and deltamethrin (see Chapter 2) are specific to these two pyrethroids. As additional information becomes available regarding adverse effects associated with low-level exposure to other pyrethroids, such information could be used to develop MRLs specific to these pyrethroids as well. See Section 3.5.2 and Chapter 4 for additional information regarding toxicological and chemical properties of Type I and Type II pyrethroids.

3.2.1 Inhalation Exposure

3.2.1.1 Death

Two case reports were located in which death was associated with allergic reactions to dog shampoo products containing pyrethrins (Wax and Hoffman 1994). An 11-year-old girl, who had been diagnosed with asthma at 6 years of age, was asymptomatic when she began to wash her dog with a shampoo containing 0.2% pyrethrin. Within 10 minutes, the subject suffered a severe acute asthmatic attack and died <3 hours later, despite medical treatment (Wagner 2000). This girl had experienced a mild increase in asthmatic symptoms when she had used the same shampoo 2 years earlier. A 37-year-old female with a 10-year history of mild asthma that did not require chronic medication, developed severe shortness of breath 5 minutes after beginning to wash her dog with a shampoo containing 0.06% pyrethrin (Wax and Hoffman 1994). The subject quickly went into cardiopulmonary arrest and died a short time later, despite efforts to revive her. Postmortem examination revealed pulmonary findings consistent with reactive airway responses. The relative contributions of inhalation and dermal exposure routes were not addressed in these reports. No other reports were located regarding death in humans following inhalation exposure to pyrethrins or pyrethroids.

Information regarding death in animals following inhalation exposure to pyrethrins or pyrethroids primarily derives from studies designed to assess lethal toxicity in animals exposed to pyrethrins or pyrethroids for durations of 2–4 hours. Hence, comprehensive dose-response data are lacking. In rats exposed to pyrethrum extract, an estimated airborne concentration in which death could be expected in 50% of the exposed animals (LC_{50}) was 3,400 mg/m^3 (Schoenig 1995). Most synthetic pyrethroids are more toxic than natural pyrethrins (the active neurotoxic components of pyrethrum extract). Results from rats exposed to synthetic pyrethroids indicate LC_{50} values ranging from approximately 23 to 1,000 mg/m^3 (Curry and Bennett 1985; Flucke and Thyssen 1980; Hext 1987; Kavlock et al. 1979; Pauluhn and Thyssen 1982). No specific patterns could be discerned regarding the relatively wide range of LC_{50} values among the various pyrethroids for which inhalation data were available. One series of studies assessed acute inhalation lethality of several Type I pyrethroids (Miyamoto 1976). In most cases, lethality was not observed following exposure to airborne pyrethroid concentrations ranging from 685 to 2,500 mg/m^3. In some cases, higher concentrations could not be attained. The only report of death was in rats and mice exposed to a mixture of (+)-allethronyl (+)-trans allethrin for 3 hours. LC_{50} values were 1,600 and 2,720 mg/m^3 for rats and mice, respectively, but minimum concentrations in which death was noted were not presented in the report. Miyamoto (1976) also assessed the toxicity of several Type I pyrethroids in rats and mice repeatedly exposed (2–4 hours/day, 5 days/week for 4 weeks) to atmospheres containing pyrethroid concentrations ranging from 6.1 to 210 mg/m^3. Although clinical signs of toxicity were noted at concentrations of 61.3 mg/m^3 (allethrin) and 200 mg/m^3 (furamethrin), mortality was not indicated.

3.2.1.2 Systemic Effects

No reports were located in which cardiovascular, gastrointestinal, musculoskeletal, renal, endocrine, dermal, or ocular effects were associated with inhalation exposure of humans or animals to pyrethrins or pyrethroids. Systemic effects related to occupational exposure are generally associated with dermal exposure to pyrethrins or pyrethroids, and are therefore presented in Section 3.2.3.2.

Respiratory Effects. Limited information was available regarding respiratory effects in humans following inhalation exposure to pyrethrins or pyrethroids. Hypersensitivity pneumonitis, characterized by pleuritic chest pain, nonproductive cough, and shortness of breath, was diagnosed in a 24-year-old woman following repeated indoor use of a pyrethrum-based insecticide (Carlson and Villaveces 1977). A pulmonary challenge test to the insecticide resulted in an itchy and runny nose within 2 minutes following initiation of exposure, but no cough or shortness of breath. Subsequent skin tests resulted in immediate skin reactions and allergic pulmonary responses to pyrethrum, but not to other ingredients in the insecticide. Signs of respiratory irritation, such as shortness of breath, cough, and congestion, were reported among five office workers, commencing upon entry into a building that had been treated for termites 2 days previously with a cypermethrin formulation that contained xylene-based aromatic petroleum solvents, trimethylbenzene, and paraffinic oils (Lessenger 1992). Symptoms worsened after the air-conditioning system was activated in an attempt to clear the air. It was determined that a portion of the insecticide had been injected into ventilation ducts. The possible influence of inert ingredients was not evaluated. Among 12 workers who sprayed lambda-cyhalothrin indoors, daily interviews following spraying on each of 6 consecutive days revealed 11 complaints of nasal irritation and 6 complaints of throat irritation (Moretto 1991). Coughing, dyspnea, increased nasal secretions, and sneezing were reported by plant nursery workers who used pyrethroids for treating conifer seedlings (Kolmodin-Hedman et al. 1982). Sniffles and sneezes were noted in subjects exposed to deltamethrin and fenvalerate while packaging the insecticides (He et al. 1988).

Signs of respiratory irritation were reported in laboratory animals acutely exposed to aerosols of pyrethroids at lethal or near-lethal airborne concentrations (Curry and Bennett 1985; Flucke and Thyssen 1980; Hext 1987; Pauluhn and Thyssen 1982). Intermediate-duration (90-day) repeated exposures of rats to mean analytical pyrethrin concentrations ≥ 30 mg/m^3 resulted in clinical and microscopic evidence of respiratory irritation; a no-effect level was 11 mg/m^3 (Schoenig 1995). More detailed information regarding respiratory effects was not available in the report.

Hematological Effects. In studies available for review, no information was located regarding hematological effects in humans following inhalation exposure to pyrethrins or pyrethroids. Available information regarding adverse hematological effects in animals is limited to a single account in which anemia was indicated in rats repeatedly exposed to pyrethrins at mean analytical airborne concentrations ≥ 30 mg/m^3 for 90 days (Schoenig 1995). More detailed information regarding hematological effects was not available in the report.

Hepatic Effects. In studies available for review, no information was located regarding hepatic effects in humans following inhalation exposure to pyrethrins or pyrethroids. Available information regarding hepatic effects in animals is limited to a single account in which increased liver weights were reported in rats repeatedly exposed to pyrethrins at a mean analytical airborne concentration of 356 mg/m^3 for 90 days (Schoenig 1995).

Body Weight Effects. In studies available for review, no information was located regarding body weight effects in humans following inhalation exposure to pyrethrins or pyrethroids. Available information regarding body weight effects in animals is limited to a single account in which decreased body weight gains were reported in rats repeatedly exposed to pyrethrins at mean analytical airborne concentrations \$100 mg/m^3 for 90 days (Schoenig 1995).

3.2.1.3 Immunological and Lymphoreticular Effects

Hypersensitivity pneumonitis, characterized by pleuritic chest pain, nonproductive cough, and shortness of breath, was diagnosed in a 24-year-old woman who was hospitalized for 2 weeks following repeated indoor use of a pyrethrum-based insecticide (Carlson and Villaveces 1977). In this patient, levels of antibodies IgG, IgM, and IgE were all elevated. Symptomatic treatment was employed, and a week after discharge, a pulmonary challenge test to the insecticide resulted in an itchy and runny nose within 2 minutes following initiation of exposure, but no cough or shortness of breath. Subsequent skin tests resulted in immediate skin reactions and allergic pulmonary response to pyrethrum, but not to other ingredients in the insecticide. In a review of literature pertaining to pyrethrum (Moore 1975), it was noted that many individuals who were sensitive to ragweed were also sensitive to pyrethrum, but that the sensitization effect arose mainly from a volatile oil contained in the pyrethrum extract, not from the pyrethrins. On the other hand, pyrethrins were implicated in two cases of severe asthmatic reactions to exposure to dog shampoo products containing pyrethrins (Wagner 2000; Wax and Hoffman 1994). A 45-year-old female animal keeper, who was suspected to be suffering from pesticide intoxication, indicated that she had been exposed to pyrethroid insecticides over a period of 13 years (Mitsche et al. 2000). Upon skin (scratch) testing, dose-dependent allergic responses (wheals and flares) were elicited from the Type I pyrethroids, S-bioallethrin and permethrin.

No animal studies were located in which inhalation exposure to pyrethrins or pyrethroids could be associated with immunological or lymphoreticular effects.

3.2.1.4 Neurological Effects

Shortness of breath, nausea, headache, and irritability were experienced by five office workers upon entering their work area 2 days after it had been sprayed with cypermethrin in an effort to eliminate termites (Lessenger 1992). The symptoms were exacerbated when the air-conditioning system was activated to ventilate the area, but levels of cypermethrin in the air were not measured. Signs of neurotoxicity have been associated with acute occupational (inhalation and dermal) exposure to various pyrethroids during outdoor or indoor spraying (Chen et al. 1991; He et al. 1991; Moretto 1991; Shujie et al. 1988; Zhang et al. 1991). In a cross-sectional survey on the prevalence of acute pyrethroid poisoning of cotton workers conducted in China in 1987 and 1988 (Chen et al. 1991), approximately 27% (696 of 2,588) of the workers who sprayed pure pyrethroids reported having experienced symptoms such as abnormal facial sensations (paresthesia), dizziness, headache, nausea, loss of appetite, blurred vision, and tightness of the chest. Eight of these workers were diagnosed with mild acute pyrethroid poisoning, characterized in part by listlessness and muscular fasciculations. He et al. (1991) reported increased peripheral nerve excitability in cotton workers following 3 days of exposure to deltamethrin during spraying. Nerve excitability was assessed by presenting two sequential electrical stimuli of equal intensity and duration to the median nerve area of the wrist and recording the median nerve activity at the lateral side of the elbow. Following deltamethrin exposure, median nerve conduction measurements revealed a significant increase in the supernormal period, defined as a period after recovery of normal excitability (from a given action potential) during which an action potential induced by a second stimulus is higher in amplitude than the first action potential. In some of these studies, air concentrations of pyrethroids in the breathing zone of the sprayers were measured and ranged from approximately 0.005 to 2.0 $\mu g/m^3$. However, one study reported air concentrations as high as 24 $\mu g/m^3$ (Shujie et al. 1988). Among sprayers, dermal contact was considered to be the major source of exposure, although some of the sprayers also reported symptoms of nasal and laryngeal irritation (Moretto 1991). Facial paresthesia, dizziness, fatigue, miliary red facial papules, and sniffles and sneezes were noted in subjects exposed to deltamethrin and fenvalerate while packaging the insecticides (He et al. 1988). Air sampling indicated pyrethroid levels in the range of 0.005–0.055 mg/m^3, but dermal contact was also evident, and may have been the basis for increased signs of toxicity during summer months.

In studies of acute lethality associated with inhalation exposure to pyrethrins or pyrethroids, neurological effects were observed at or near lethal exposure levels. However, most studies do not include dose-response data for exposure levels much lower than those resulting in death. Tremors were observed in rats acutely exposed to pyrethrins at mean analytical airborne concentrations $2,100 mg/m³, but not at a concentration of 690 mg/m³ (Schoenig 1995). Acute exposure of rats to aerosols of a 13% formulation of cyhalothrin, at analytical concentrations ranging from 3.6 to 68 mg/m³, resulted in dose-related increasing severity of neurological signs, ranging from temporary lethargy, abnormal posture, and salivation at the lowest concentration, to convulsions and death within 15 minutes postexposure at the highest concentration (Curry and Bennett 1985). Disturbed posture and abnormal motor activity were observed in rats exposed to aerosols of cyfluthrin for 4 hours at an analytical concentration of 17 mg/m³, the lowest level presented. A concentration of 735 mg/m³, which was lethal to many of the rats, caused severe behavioral disturbances in surviving rats that continued for 3 days postexposure (Pauluhn and Thyssen 1982). A group of female rats exhibited no signs of toxicity in response to acute exposure to cyfluthrin at an analytical concentration of 44 mg/m³ (Flucke and Thyssen 1980). Both male and female rats, similarly exposed to a concentration of 57 mg cyfluthrin/m³, showed signs of restlessness and altered gait. Labored breathing, hyperactivity, and tremors were reported in rats repeatedly exposed (6 hours/day, 5 days/week for 90 days) to pyrethrins at a mean airborne concentration of 356 mg/m³ (Schoenig 1995). Repeated 6-hour inhalation exposures to atmospheres containing cyfluthrin concentrations of 10.5 mg/m³ or higher resulted in dose-related unspecified clinical signs of behavioral disorders (Flucke and Thyssen 1980; Thyssen 1980).

No reports were located regarding the following health effects in humans or animals following inhalation exposure to pyrethrins or pyrethroids:

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

3.2.2 Oral Exposure

3.2.2.1 Death

Among 573 cases of acute pyrethroid poisoning reported in China between 1983 and 1988, 344 cases with accidental poisoning were considered to have been largely due to ingestion of pyrethroids (He et al. 1989). Four deaths were reported; two of these were related to occupational exposure. Peter et al. (1996) reported death in a 30-year-old male approximately 2 days after he had consumed about 30 mL of deltamethrin. In another case, an adult male rapidly developed convulsions, became comatose, and died shortly after having accidently ingested an unknown amount of 10% cypermethrin (Poulos et al. 1982). No other information was located regarding death in humans following oral exposure to pyrethrins or pyrethroids.

Animal studies associate mortality with relatively high oral exposure to pyrethrins and pyrethroids. Acute oral LD_{50} values for total pyrethrins from undiluted pyrethrum extract were 2,370 and 1,030 mg/kg in male and female rats, respectively (Schoenig 1995). Acute oral LD_{50} values for pyrethroids in rats range from approximately 18 to >5,000 mg/kg (Casida et al. 1983; Metcalf 1995; Valentine 1990). The wide range in LD_{50} values is dependent on a number of factors including specific pyrethroid, ratios of stereo and optical isomers within a given pyrethroid formulation, and vehicle. Acute oral LD_{50} values are generally lower in Type II than Type I pyrethroids, indicating a greater degree of toxicity for Type II pyrethroids. Pyrethroid-induced mortality appears to be influenced by ambient temperature. Acute oral LD_{50} values for cismethrin in female rats increased from 157 mg/kg at 4 EC to 197 mg/kg at 20 EC and >1,000 mg/kg at 30 EC (White et al. 1976). In a 4-week oral study, mortality was observed in rats after 3–5 days of daily oral administration of cyfluthrin at a dose level of 80 mg/kg/day (Flucke and Schilde 1980). In mice, repeated administration of fenvalerate, at a dose level of 80 mg/kg/day, also resulted in mortality that was considered to be compound related (Cabral and Galendo 1990). In 90-day oral studies, compound-related death was noted in rats and mice given diets containing pyrethrins at concentrations $10,000 ppm (800 and 1,900 mg/kg/day for rats and mice, respectively) (Schoenig 1995). Compound-related mortality was also reported in pregnant rats and rabbits repeatedly administered oral doses of pyrethrins (in 0.5% methyl cellulose) $150 and 600 mg/kg/day, respectively (Schoenig 1995). Three of four dogs died during an 8-week oral study in which pyrethrins were administered in the diet at a concentration of 6,000 ppm (approximate dose of 100 mg/kg/day) (Schoenig 1995). One of six dogs, administered 1,000 ppm of fenvalerate in the diet (approximate dose of 80 mg/kg/day), was euthanized *in extremis* during week 24 after exhibiting signs of extreme neurotoxicity (Parker et al. 1984b). One of six dogs, given daily oral doses of cyhalothrin at 3.5 mg/kg, was killed during week 46 of a 52-week oral dosing study, due to persistent pyrethroid-induced convulsions (Hext et al. 1986). Mortality was also observed during a 90-day oral exposure to permethrin in the diets of rats (DOD 1977). All 10 male and female rats in the projected 850 mg/kg/day exposure groups died during the study; actual doses were 505 and 870 mg/kg/day in males and females, respectively. Mortality was not significantly increased in rats or mice administered permethrin in the diet at concentrations resulting in estimated daily doses of up to 104 mg/kg/day for 2 years in rats or 350 mg/kg/day for 98 weeks in mice (Ishmael and Litchfield 1988).

Selected LD_{50} values for some pyrethroids are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

No reports were located regarding respiratory, cardiovascular, musculoskeletal, dermal, or ocular effects following oral exposure of humans or animals to pyrethrins or pyrethroids.

Gastrointestinal Effects. Information regarding gastrointestinal effects following oral exposure is limited to clinical signs following exposure to pyrethroids. Symptoms such as epigastric pain, nausea, vomiting, and diarrhea have been reported in human subjects who consumed relatively large quantities of pyrethroids (Gotoh et al. 1998; He et al. 1989). Vomiting and diarrhea were reported in dogs ingesting pyrethroids in the diet at dose levels as low as 1–6 mg/kg/day for up to 13 weeks (IRIS 2001a, 2001b).

Hematological Effects. Information regarding hematological effects following oral exposure is limited. Leukocytosis was observed in 15% of 235 human cases of pyrethroid poisoning in which blood tests were performed (He et al. 1989). In most animal studies that examined hematological end points, no significant alterations were observed. However, Shakoori et al. (1992a) reported significantly decreased red blood cell count, hemoglobin content, and mean corpuscular hemoglobin, as well as increased white blood cell count in rabbits following daily oral administration of fenvalerate at a dose level of 10 mg/kg for 7 days. Schoenig (1995) reported evidence of anemia in surviving dogs that were fed pyrethrins in the diet for 8 weeks at a concentration resulting in a dose level of approximately 100 mg/kg/day. In a 6-month feeding study in dogs, decreased red blood cell counts and decreased hematocrit and hemoglobin were observed at a dietary concentration of fenpropathrin that resulted in a dose level of approximately 20 mg/kg/day (Parker et al. 1984b). Hematology and blood chemistry data from rats and mice, administered permethrin in the diet at concentrations resulting in estimated doses of up to 104 mg/kg/day for 2 years (rats) or 350 mg/kg/day for 98 weeks (mice), did not indicate significant treatment-related hematological effects (Ishmael and Litchfield 1988).

Table 3-1. Levels of Significant Exposure to Pyrethrins and Pyrethroids - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL: Less Serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	once (G)				3801 F (LD_{50})	DOD 1977 Permethrin (45/55 cis/trans)
2	Rat (Sprague-Dawley)	once (GO)				383 M (LD_{50})	DOD 1977 Permethrin (45/55 cis/trans)
3	Rat (Long- Evans)	once (G)				4892 M (LD_{50}) 2712[b] F (LD_{50})	DOD 1977 Permethrin (45/55 cis/trans)
4	Rat (Sprague-Dawley)	once (GO)				584 M (LD_{50})	DOD 1977 Permethrin (45/55 cis/trans)
5	Rat (Sprague-Dawley)	14 d (F)				699[b] M (death in 6/6) 769 F (death in 5/6)	DOD 1977 Permethrin (45/55 cis/trans)
6	Rat (Long- Evans)	14 d (F)				515 F (death in 3/6 in first 5 days)	DOD 1977 Permethrin (45/55 cis/trans)
7	Rat (NS)	once (GO)				413 F (LD_{50})	DOD 1977 Permethrin (45/55 cis/trans)
8	Rat (CD)	once 4 hr (NS)				2370 M (LD_{50}) 1030[b] F (LD_{50})	Schoenig 1995 Pyrethrum extract

Table 3-1. Levels of Significant Exposure to Pyrethrins and Pyrethroids - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
9	Rat (Long- Evans)	14 d (F)	Hepatic		218 F (increased liver-to-body weight ratio)		DOD 1977 Permethrin (45/55 cis/trans)
10	Rat (Sprague-Dawley)	14 d (F)	Hepatic	186[b] M 210 F	379 M (increased liver-to-body 369[b] F weight ratio)		DOD 1977 Permethrin (45/55 cis/trans)
	Neurological						
11	Rat (Sprague-Dawley)	14 d (F)		186[b] M 210 F		379 M (muscle tremors) 369[b] F (muscle tremors)	DOD 1977 Permethrin (45/55 cis/trans)
12	Rat (Long- Evans)	14 d (F)		92[b] M 114 F		185[b] M (muscle tremors) 218 F (muscle tremors)	DOD 1977 Permethrin (45/55 cis/trans)
13	Rat (CD)	once (NS)		710 M 320[b] F			Schoenig 1995 Pyrethrum extract
	Developmental						
14	Mouse (NMRI)	ppd 10-16 1x/d (G)			0.21[c] M (increase in spontaneous activity and decrease in muscarinic receptors in cerebral cortex at 4 months)		Ahlbom et al. 1994 Bioallethrin

Table 3-1. Levels of Significant Exposure to Pyrethrins and Pyrethroids - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
15	Mouse (NMRI)	ppd 10-16 1x/d (G)			0.7 M (increase in spontaneous activity and decrease in muscarinic receptors in cerebral cortex at 4 months)		Eriksson and Fredriksson 1991 Bioallethrin
16	Mouse (NMRI)	ppd 10-16 1x/d (G)			0.7[d] M (increase in spontaneous activity and decrease in muscarinic receptors in cerebral cortex at 4 months)		Eriksson and Fredriksson 1991 Deltamethrin
17	Mouse NMRI	ppd 10-16 1x/d (G)			0.72 (changes in density of brain muscarinic and nicotinic receptor sites)		Eriksson and Nordberg 1990 Bioallethrin

Table 3-1. Levels of Significant Exposure to Pyrethrins and Pyrethroids - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
INTERMEDIATE EXPOSURE							
Death							
18	Rat (Sprague-Dawley)	90 d (F)				505[b] M (death in 10/10) 870 F (death in 10/10)	DOD 1977 Permethrin (45/55 cis/trans)
Systemic							
19	Rat (Sprague-Dawley)	90 d (F)	Hepatic	73.6[b] M 76.3 F	243.5[b] M (increased liver-to-body 250.7 F weight ratio)		DOD 1977 Permethrin (45/55 cis/trans)
Reproductive							
20	Rat (albino)	65 d 1x/d (GW)				1 M (50% reduction in successful impregnation)	Abd El-Aziz et al. 1994 Deltamethrin
Developmental							
21	Rat (Wistar)	Gd 4-21 1x/day (GO)			15 B (increased levels of muscarinic receptors in striatal membrane)		Malaviya et al. 1993 Cypermethrin
22	Rat (Wistar)	Gd 4-21 1x/day (GO)			10 B (decreased levels of dopamine receptors in striatal membrane)		Malaviya et al. 1993 Fenvalerate
23	Rat (Wistar)	Gd 4-21 Ld 1-21 1x/day (GO)			10 B (increased levels of dopamine and muscarinic receptors in striatal membrane)		Malaviya et al. 1993 Fenvalerate

Table 3-1. Levels of Significant Exposure to Pyrethrins and Pyrethroids - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
24	Rat (Wistar)	Gd 4-21 Ld 1-21 1x/day (GO)			15 B (increased levels of dopamine and muscarinic receptors in striatal membrane)		Malaviya et al. 1993 Cypermethrin

Table 3-1. Levels of Significant Exposure to Pyrethrins and Pyrethroids - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Neurological						
25	Rat (Wistar)	2 yr (F)		37.5 M		187.2 M (slight whole body tremors during first 2 weeks)	Ishmael and Litchfield 1988 Permethrin (40/60 cis/trans)
26	Rat (Sprague-Dawley)	104 wk (F)		17[b] M 20 F		70 M (abnormal gait, muscular incoordination)	Parker et al. 1984a Fenvalerate
27	Mouse (Swiss)	2 yr (F)		295.1 M 348.1[b] F			Ishmael and Litchfield 1988 Permethrin (40/60 cis/trans)
28	Dog (Beagle)	52 wk 1x/d (GO)		0.5 M F		3.5 M (muscle tremors, ataxia) F	Hext et al. 1986 Cyhalothrin

[a]The number corresponds to entries in Figure 3-1.
[b]Differences in levels of health effects and cancer effects between males and females are not indicated in figure 3-1. Where such differences exist, only the levels of effects for the most sensitive gender are presented.
[c]Used to derive an acute oral minimal risk level (MRL) of 0.0007 mg/kg/day for bioallethrin. The MRL was derived by dividing the LOAEL by an uncertainty factor of 300 (3 to account for intrahuman variability, 10 for interspecies variability, and 10 for the use of a LOAEL).
[d]Used to derive an acute oral minimal risk level (MRL) of 0.002 mg/kg/day for deltamethrin. The MRL was derived by dividing the LOAEL by an uncertainty factor of 300 (3 to account for intrahuman variability, 10 for interspecies variability, and 10 for the use of a LOAEL).

B = both; d = day(s); (F) = feed; F = female; (G) = gavage; Gd = gestation day; (GO) = gavage in oil; (GW) = gavage in water; hr = hour(s); LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mg/kg/day = milligram per kilogram per day; NOAEL = no-observed-adverse-effect level; (NS) = not specified; ppd = post-parturition day; wk = week(s); x = time; yr = year(s)

Figure 3-1. Levels of Significant Exposure to Pyrethrins and Pyrethroids - Oral

Acute (≤14 days)

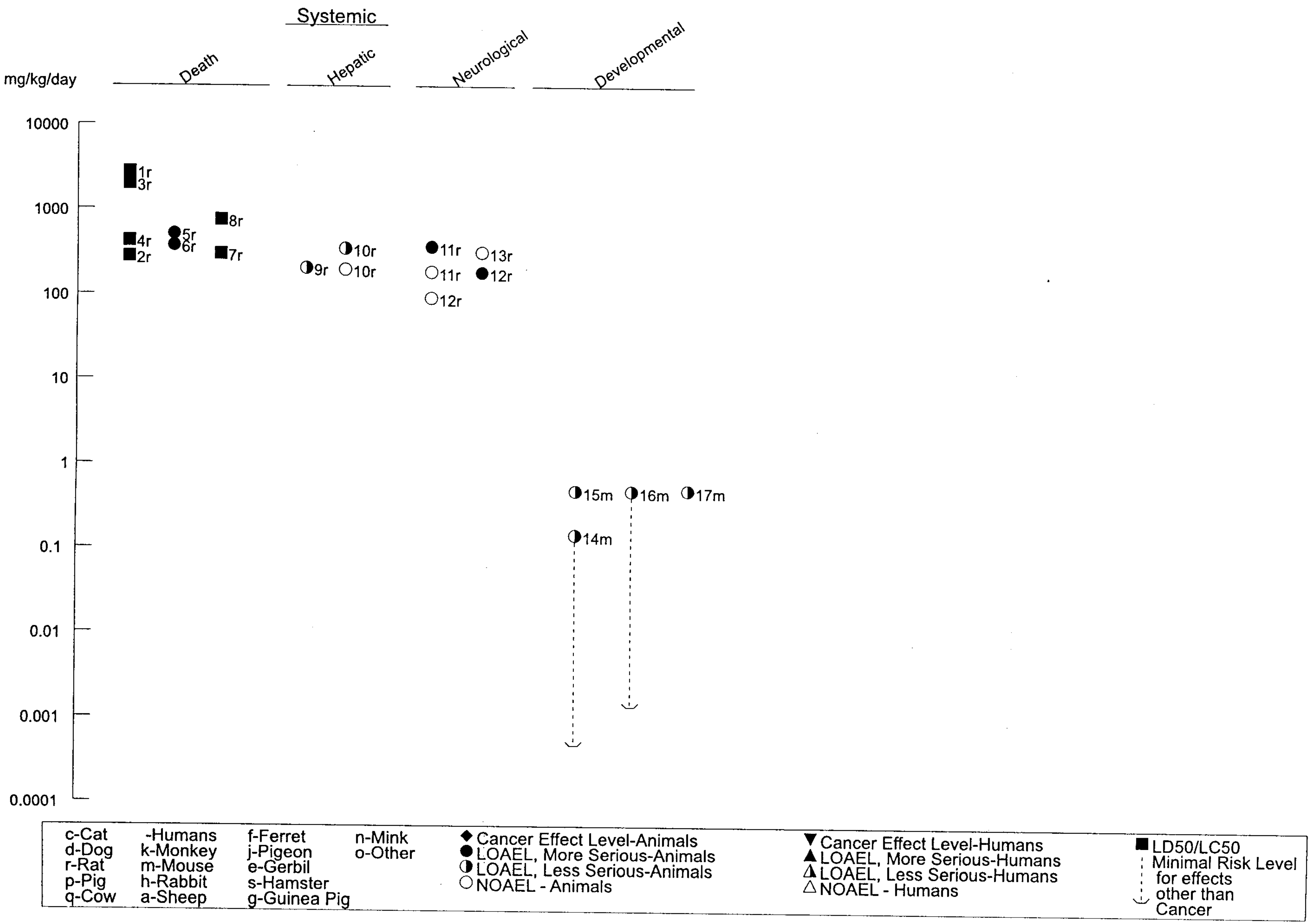


Figure 3-1. Levels of Significant Exposure to Pyrethrins and Pyrethroids - Oral (*continued*)

Intermediate (15-364 days)

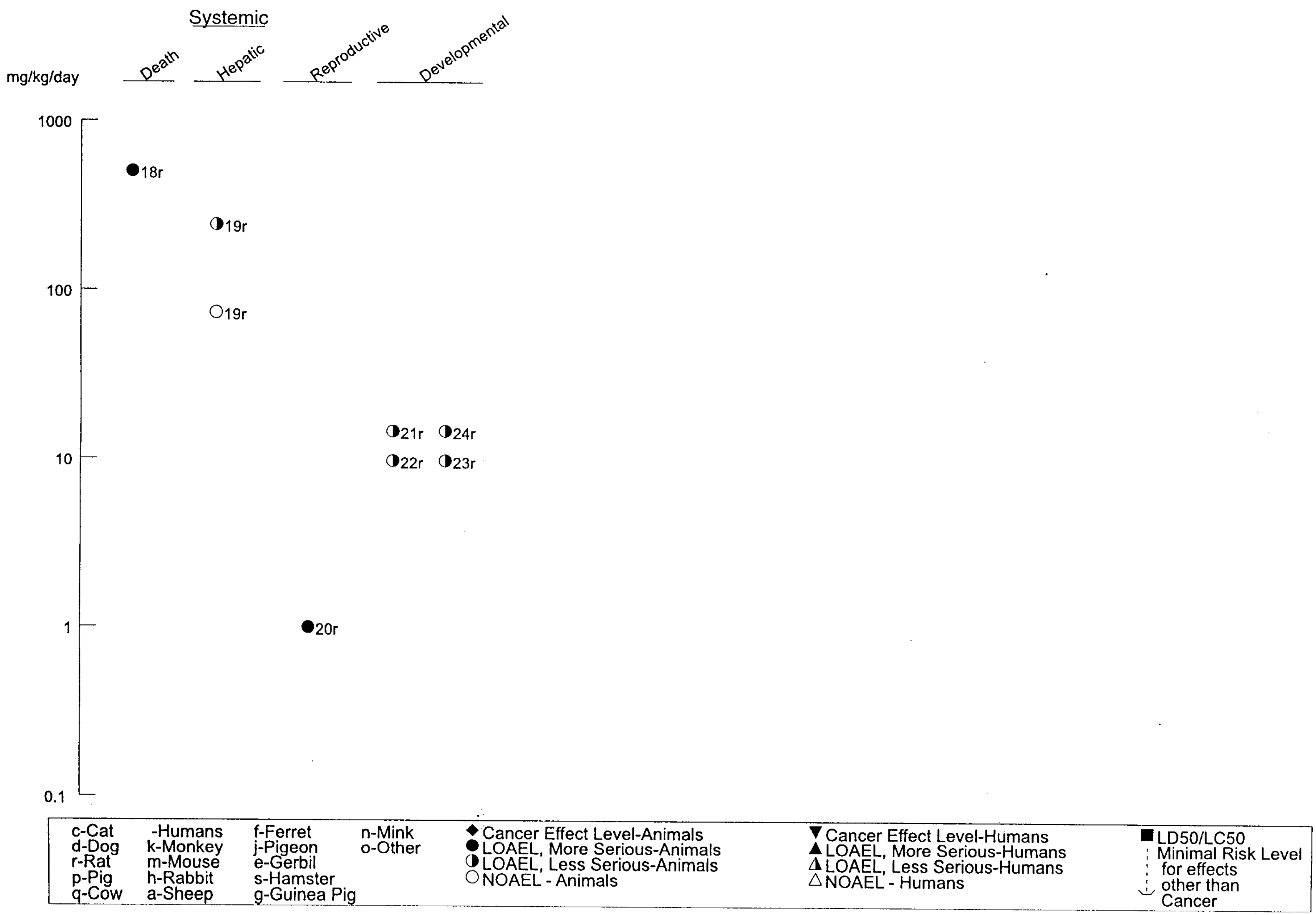
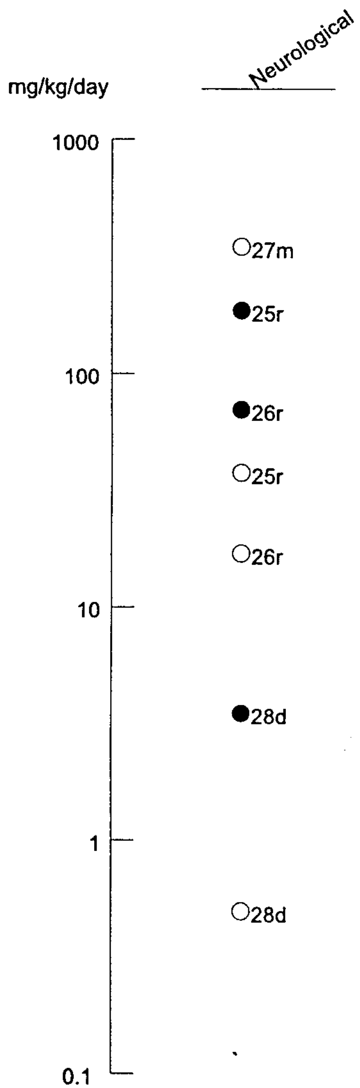


Figure 3-1. Levels of Significant Exposure to Pyrethroids - Oral (*continued*)

Chronic (≥365 days)



c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Hepatic Effects. No studies were located regarding hepatic effects in humans following oral exposure to pyrethrins or pyrethroids. Some animal studies indicated increased liver weights, congestion, hepatocellular hypertrophy, and other microscopic signs of liver changes in laboratory animals during intermediate- and chronic-duration oral exposure to pyrethrins or pyrethroids, particularly at dose levels also resulting in clinical signs of neurotoxicity (Hext et al. 1986; IRIS 2001c, 2001d; Ishmael and Litchfield 1988; Parker et al. 1984a, 1984b; Schoenig 1995). These hepatic effects may reflect, at least in part, an adaptive response similar to that seen following exposure to many other xenobiotics (Ishmael and Litchfield 1988; Okuno et al. 1986a). Increased activities of the liver enzyme, SGPT, were noted in serum of dogs given pyrethrins in the diet at a concentration of 2,500 ppm (Schoenig 1995).

Renal Effects. No studies were located regarding renal effects in humans following oral exposure to pyrethrins or pyrethroids. Available information regarding renal effects in animals is limited to a report of decreased kidney weights and tubular degeneration in rats consuming pyrethrins (from pyrethrum extract) in the diet at concentrations resulting in dose levels $320 mg/kg/day for 90 days (Schoenig 1995), and a report of a small decrease in kidney weight in male rats receiving permethrin in the diet at concentrations resulting in estimated daily doses of 19.4–91.5 mg/kg for 2 years (Ishmael and Litchfield 1988). However, the magnitude and statistical significance of these renal changes were not presented in these reports. In a 2-year feeding study reported by Sumitomo Chemical America, Inc., and summarized in IRIS (2001b), increased absolute and relative kidney weights were observed in male (but not female) rats fed fenpropathrin (in corn oil) at a dietary concentration of 600 ppm (calculated daily doses of 22.8 and 23.98 mg/kg for males and females, respectively).

Endocrine Effects. No studies were located regarding endocrine effects in humans following oral exposure to pyrethrins or pyrethroids. Limited data were available regarding endocrine effects in animals following oral exposure to pyrethroids. Serum levels of the thyroid hormones T_3 and T_4 were significantly decreased in mice administered fenvalerate at a dose level of 120 mg/kg/day for 15 days (Maiti and Kar 1998). Akhtar et al. (1996) reported similar effects in rats administered bifenthrin or lambda-cyhalothrin at daily oral dose levels of 0.5 mg/rat (approximately 0.75 mg/kg/day) and 0.2 mg/rat (approximately 2 mg/kg/day), respectively, for 21 days. Lambda-cyhalothrin treated rats also exhibited a significantly decreased serum T_3/T_4 ratio, relative to controls. In addition, both bifenthrin and lambda-cyhalothrin treatment resulted in significantly increased serum TSH levels, compared with control rats. The studies of Maiti and Kar (1998) and Akhtar et al. (1996) did not include dose-response information, nor were thyroid tissues examined. However, these studies indicate that exposure to pyrethroids may result in changes in endocrine function. Pyrethroid-induced decreased plasma testosterone may also serve as an indication of potential for pyrethroid-mediated endocrine effects. Significantly reduced plasma testosterone levels were noted as early as day 14 in groups of male rats administered deltamethrin in oral doses of 1 or 2 mg/kg for 65 days, and remained lower than controls throughout 21 days of posttreatment observation (Abd El-Aziz et al. 1994). El-Khalek et al. (1999) observed significant decreases in plasma testosterone levels in rats administered cypermethrin in oral doses of 3.8 or 7.7 mg/kg/day for 65 days, also demonstrating that this effect lasted throughout 30 days of posttreatment observation. In a 2-year feeding study reported by Sumitomo Chemical America, Inc., and summarized in IRIS (2001b), absolute and relative pituitary weights were nearly doubled in male rats fed fenpropathrin (in corn oil) at a dietary concentration of 600 ppm (calculated daily dose of 22.8 mg/kg). Female rats of the 600 ppm group (calculated daily dose of 23.98 mg/kg) exhibited decreased absolute and relative ovary weights.

Body Weight Effects. No studies were located regarding body weight effects in humans following oral exposure to pyrethrins or pyrethroids. Reduced body weights or body weight gains were reported in some studies of laboratory animals administered pyrethrins (from pyrethrum extract) for intermediate or chronic durations (Schoenig 1995). For instance, decreased body weight gain and food consumption were observed in rats administered 3,000–20,000 ppm (total pyrethrins; approximately 320–1,600 mg/kg/day) in the diet for 90 days. Decreased body weight and food consumption were also noted in dogs administered total pyrethrins at 6,000 ppm (approximately 100 mg/kg/day) in the diet for 8 weeks. Decreased body weight was also reported in rats administered total pyrethrins at 3,000 ppm (approximately 250 mg/kg/day) in the diet for 104 weeks. Weight loss was observed in rabbit does administered 600 mg total pyrethrins/kg/day on gestation days 7–19. In a 2-generation reproductive toxicity study involving dietary exposure, decreased body weights and food consumption were observed in F_1 parental rats that had been exposed to pyrethrins during fetal and neonatal development, as well as premating, mating, and gestation. The reports of Schoenig (1995) did not include more detailed descriptions of body weight effects at dose levels that also resulted in clinical signs of neurotoxicity (Ishmael and Litchfield 1988; Parker et al. 1984a; Schoenig 1995).

The EPA (IRIS 2001b) reviewed a report by Sumitomo Chemical America, Inc. (report not currently available to ATSDR) in which slightly reduced weight gain was noted in dogs administered fenpropathrin in the diet at dose levels $500 ppm (12.5 mg/kg/day) for 3 months. Ishmael and Litchfield (1988) reported small but significant decreased body weight gains in rats and mice administered permethrin at 2,500 ppm in the diet for 2 years (rats) or a lifetime (mice), in the absence of apparent changes in food consumption. Estimated daily doses of permethrin were 91.5 and 103.8 mg/kg/day for male and female rats, respectively, and 295.1 and 348.1 mg/kg/day for male and female mice, respectively, based on body weight and food consumption values presented. The decreased body weight gain was seen only during the first 6 weeks of treatment in rats and sporadically during the first 52 weeks of treatment in mice. Parker et al. (1984a) observed significant decreases in mean body weight gain among rats fed fenvalerate at 1,000 ppm in the diet (approximate doses of 70 and 80 mg/kg/day for males and females, respectively) from week 16 (males) and week 44 (females) through week 104. No treatment-related changes in food consumption were observed, and no treatment-related significant changes in body weight were seen in groups receiving #250 ppm of fenvalerate in the diet, relative to controls.

3.2.2.3 Immunological and Lymphoreticular Effects

No reports were located in which immunological or lymphoreticular effects in humans could be specifically associated with oral exposure to pyrethrins or pyrethroids. See Section 3.2.1.3 for information regarding immunological effects in humans following exposures to pyrethrins or pyrethroids that were likely mixed (inhalation, dermal, and possibly oral).

Information on immunotoxicity of selected pyrethroids is available from oral studies in rats, mice, and rabbits repeatedly administered pyrethroids at doses low enough that clinical signs of neurotoxicity were not observed (Blaylock et al. 1995; Demian 1998; Demian and El-Sayed 1993; Dési et al. 1986; Lukowicz-Ratajczak and Krechniak 1992). In rats, a single oral dose of cypermethrin at 125 mg/kg resulted in statistically significant changes, which included suppression of the humoral immune response, decreases in rosette-forming lymphocytes and ratio of lymphocytes to leukocytes, and decreased relative spleen weight. Although doses of cypermethrin at 6.25, 12.5, or 25 mg/kg/day for 6 or 12 weeks did not result in significant changes in relative spleen weight, a significantly reduced humoral immune response was observed at the 25 mg/kg/day dose level, and both the 12.5 and 25 mg/kg/day levels resulted in significant decreases in rosette-forming lymphocytes (Dési et al. 1986). Dose-dependent significant suppression of the humoral immune response in rabbits was observed by the end of week 1 of a study in which cypermethrin was administered orally to rabbits 5 days/week for 6 weeks at levels of 75, 150, or 300 mg/kg/day (Dési et al. 1986).

Lukowicz-Ratajczak and Krechniak (1992) administered deltamethrin to mice in oral doses of 6 mg/kg/day for 84 days or 15 mg/kg/day for 14 days. Treatment at both dose levels resulted in significant immunosuppression of the humoral immune response and a significant decrease in enzyme activity in lymphocytes isolated from the lymph nodes and spleen. These effects occurred earlier in the treatment period in high-dose mice. Other signs of immunotoxicity included decreased numbers of splenic plaque-forming cells, decreased percentages of rosette-forming lymphocytes in lymph nodes and spleen, depressed cell-mediated immune response that was expressed as decreased swelling of the foot pad in response to deltramethrin exposure of mice previously immunized with sheep red blood cells, and decreased interleukin-1 activity.

Demian and coworkers (Demian 1998; Demian and El-Sayed 1993) demonstrated dose-related deltamethrin-induced suppression of the humoral immune response, decreased numbers of splenic plaque-forming cells and rosette-forming lymphocytes, decreased total serum protein (as well as alpha-1-, alpha-2-, and gamma-globulins), and increased serum albumin content. Doses used by Demian and coworkers were described as being 0.1 and 0.2 of the oral LD_{50} value, but this value was not identified in the reports.

Blaylock et al. (1995) assessed the immunotoxic potential of permethrin by examining immune responses of splenocytes from mice that had been administered permethrin at 0–0.4 mg/kg/day (0–1% of the oral LD_{50} value) for 10 days. At the highest dose tested (0.4 mg/kg/day), significantly reduced mixed lymphocyte responses, T-lymphocyte cytotoxic activity, and natural killer cell activity were observed. No significant treatment-related changes were seen in spleen weights.

Severe leukopenia was observed in rats orally administered cypermethrin at 40 mg/kg/day for 90 days (Varshneya et al. 1992). A delayed type skin hypersensitivity test, performed on day 61 (following intradermal injection of tuberculin on day 60), revealed 24 and 27% decreases in reactivity in the 20 and 40 mg/kg/day dose groups, respectively. Examination of organ weights revealed a significant decrease in relative spleen weight within the high-dose group. However, no definite treatment-induced effect was noticed in the humoral immune response. Madsen et al. (1996) reported increased numbers of antibody forming cells in the spleen and enhanced natural killer cell activity in rats administered deltamethrin at oral dose levels of 5 or 10 mg/kg/day for 28 days. See Section 3.2.2.6 for information regarding immunological effects in rats exposed via their mothers during gestation.

The highest NOAEL values and all LOAEL values from each reliable study for immunological and lymphoreticular effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.4 Neurological Effects

In cases of accidental or intentional ingestion of relatively large quantities of solutions containing pyrethroids, neurotoxic signs such as headache, muscular fasciculations, convulsions, and coma have been reported (Gotoh et al. 1998; He et al. 1989; Peter et al. 1996).

Numerous investigators have reported signs of neurotoxicity in laboratory animals administered lethal and sublethal oral doses of pyrethrins and pyrethroids. Two different types of pyrethroids are recognized, based on symptoms of poisoning and chemical structure (Coats 1990; Verschoyle and Aldridge 1980). Chapter 4 contains information regarding chemical properties of Type I and Type II pyrethroids. Type I pyrethroids induce neurological signs that include aggressive behavior and increased sensitivity to external stimuli, fine tremor, prostration with coarse whole body tremor, elevated body temperature, and coma. Pyrethrins induce neurological effects similar to those induced by Type I pyrethroids (Mbaria et al. 1993; Schoenig 1995). Effects induced by Type II pyrethroids include pawing and burrowing behavior, profuse salivation, increased startle response, abnormal hind limb movements, and coarse whole body tremor that progresses to sinuous writhing (choreoathetosis). The presence of a cyano group within Type II pyrethroids also distinguishes this group from Type I pyrethroids. However, fenpropathrin and cyphenothrin, which are considered to be Type II pyrethroids by the presence of a cyano group, induce intermediate neurological responses characterized by both tremors (typical of Type I pyrethroids) and salivation (typical of Type II pyrethroids) (Miyamoto et al. 1995; Wright et al. 1988).

Acute oral dosing with Type I or Type II pyrethroids results in typical clinical signs of neurotoxicity within 20 minutes to 1 hour, with symptoms subsiding within several hours to a few days (Eriksson and Nordberg 1990; Hudson et al. 1986; Parker et al. 1983, 1984a, 1984b, 1985; Ray and Cremer 1979; Southwood 1984). Refer to Section 3.5.2 for a detailed discussion of mechanisms of toxicity associated with exposure to Type I and Type II pyrethroids. Several investigators reported typical signs of Type I or Type II pyrethroid poisoning in laboratory animals during repeated oral administration of pyrethrins or pyrethroids (from 2 days to 2 years), but there were few indications that repeated or continuous exposure might result in cumulative neurological effects (Cabral and Galendo 1990; DOD 1977; Flucke and Schilde

1980; Hext et al. 1986; IRIS 2001a, 2001b; Ishmael and Litchfield 1988; Mohan et al. 1998; Parker et al. 1984a, 1984b; Schoenig 1995). For example, Ishmael and Litchfield (1988) administered permethrin in the diet of rats and mice for 2 years and a lifetime (up to 98 weeks), respectively. Male and female rats were administered permethrin at concentrations that resulted in daily doses of 19.4, 37.5, and 91.5 mg/kg/day and 19.1, 40.2, and 103.8 mg/kg/day, respectively. Estimated doses to male and female mice were 28.7, 124.2, and 295.1 mg/kg/day and 42.8, 135.8, and 348.1 mg/kg/day, respectively. During the first 2 weeks of treatment, high-dose male and female rats exhibited slight whole body tremors, hypersensitivity to noise and other disturbances, and piloerection. These findings were not seen at lower dose levels. None of the groups of mice exhibited clinical signs of treatment-related neurotoxicity. Histological and ultrastructural examination of sciatic nerves at interim (52 weeks in rats, 26 and 52 weeks in mice) and terminal kills revealed no signs of permethrin-induced abnormalities. In a cancer bioassay, Cabral and Galendo (1990) administered fenvalerate (in arachis oil vehicle) to mice via gavage at 0, 40, or 80 mg/kg/day for 2 years. Reported noncancer effects were limited, but included observation of choreoathetosis and salivation in high-dose female mice. Parker et al. (1984a) fed rats fenvalerate at dietary concentrations ranging from 1 to 1,000 ppm (0.07–70 mg/kg/day in males and 0.08–80 mg/kg/day in females) for 2 years. Five of 50 high-dose male rats exhibited clinical signs of neurotoxicity (abnormal gait, ataxia, muscular incoordination) during weeks 3 and 4. There was no report of clinical signs of neurotoxicity in other treatment groups.

Crofton et al. (1995) demonstrated the significance of vehicle in the expression of neurological effects in rats given single oral doses of deltamethrin. The lowest doses at which at least 50% of the exposed animals exhibited decreased motor activity (ED_{50}) ranged from 5.1 mg/kg for deltamethrin in corn oil to >1,000 mg/kg for deltamethrin in methyl cellulose.

Some investigators have assessed other aspects of neurotoxicity in animals administered oral doses of pyrethroids, often at doses much lower than those resulting in typical clinical signs. For example, Crofton and Reiter (1988) observed significant decreases in motor activity of rats following administration of a Type I pyrethroid (permethrin) at 200 mg/kg and Type II pyrethroids (cyfluthrin at 12.5 mg/kg, fenvalerate at 30 mg/kg, flucythrinate at 2.5 mg/kg, cypermethrin at 30 mg/kg, fluvalinate at 15 mg/kg, and a pyrethroid identified as RU26607 at 3 mg/kg). Crofton and Reiter (1988) also found that some of the pyrethroids tested affected the acoustic startle response by altering the amplitude or latency. In another rat study, a Type I pyrethroid (NAK 1901) enhanced the acoustic startle response amplitude in a dose-dependent manner, whereas a Type II pyrethroid (cypermethrin) had no effect on amplitude or latency, even at a dose level that elicited clinical signs (Hijzen et al. 1988). Moniz et al. (1994) administered cyhalothrin to rat dams (0.02% in the drinking water, a level that did not elicit clinical signs) during lactation of pups. At 21 days of age, motor activity of pups exposed to cyhalothrin via their mothers was not significantly different from that observed in control pups. However, when trained and tested for inhibitory avoidance behavior at the age of 90 days, pups in the cyhalothrin treatment group exhibited decreased active avoidance and operant conditioned responses. Reduced locomotion and rearing frequency were observed in rats administered fenvalerate at single oral doses of 10 mg/kg (Spinosa et al. 1999). No treatment-related effects were seen in passive avoidance. Husain et al. (1991) observed pronounced treatment-related changes in brain levels of the neurotransmitters noradrenalin and dopamine, as well as their acid metabolites, following oral administration of fenvalerate at doses of 5–20 mg/kg/day for 21 days. The changes did not appear to be either dose-related or region specific, although the brain regions most affected appeared to be those that contribute most significantly to motor function and aggression. Significant increases were noted in grouped total activity and individual nonambulatory (but not ambulatory) activity of male mice observed for 4 hours following single oral administration of permethrin at 50 mg/kg or fenvalerate at 30 mg/kg (Mitchell et al. 1988). These effects were observed in the absence of typical clinical signs of pyrethroid-induced neurotoxicity. In another set of behavioral paradigms in mice, fenvalerate, administered in single oral doses of 15–45 mg/kg (as little as 1/24 of the LD_{50} value), resulted in significantly increased startle response latency and decreased ambulation and rearing in open field (Mandhane and Chopde 1997). Dose-related increased immobility in tail-suspension test and attenuated haloperidol-induced catalepsy were also observed. Axonal damage was observed in peripheral nerves of laboratory animals that had been administered pyrethroids in oral doses sufficient to induce clinical signs of neurotoxicity; the damage resolved upon cessation of treatment (Calore et al. 2000; Parker et al. 1985; Rose and Dewar 1983). Although the typical primary Type I and Type II clinical responses to pyrethroid poisoning can be explained by the action of Type I and Type II pyrethroids on sodium channels, the basis for these other pyrethroid-associated neurological changes is not presently known (see Section 3.5.2 for a discussion of mechanisms of toxicity). See Section 3.2.2.6 for information regarding neurodevelopmental effects in mice administered pyrethroids during neonatal development.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.5 Reproductive Effects

No reports were located regarding reproductive effects in humans following oral exposure to pyrethrins or pyrethroids.

No signs of exposure-related adverse effects on reproductive parameters, including male or female fertility indices, litter size, and numbers of viable and stillborn pups, were observed in a 2-generation reproductive study of rats administered pyrethrins (from pyrethrum extract) in the diet at concentrations up to 3,000 ppm (resulting in an average daily dose of approximately 240 mg/kg) (Schoenig 1995). No signs of reproductive toxicity were observed in a 3-generation reproductive toxicity study of fenpropathrin administered in the diet at concentrations up to 250 ppm (resulting in an average daily dose of approximately 25 mg/kg) (Hend et al. 1979). In another 3-generation reproductive toxicity study, rats were administered cyfluthrin in the diet at concentrations of 50, 150, or 450 ppm (resulting in average daily doses of 4, 11–14, or 35–40 mg/kg/day, respectively, in males and 5.5, 14–16, or 46–50 mg/kg/day, respectively, in females) (Loeser and Eiben 1983). Treatment-related reduced viability, decreased lactation, and decreased birth weight or weight gain were observed in some generations at concentrations ≥150 ppm.

Intermediate-duration oral administration of pyrethroids to male laboratory animals at dose levels well below those eliciting clinical signs of neurotoxicity have resulted in adverse effects in male reproductive organs. Abd El-Aziz et al. (1994) found that male rats, administered deltamethrin in oral doses as low as 1 mg/kg/day (the lowest level tested) for 65 days, exhibited significantly lower weights of testicles, seminal vesicles, and prostate gland than vehicle controls. Sperm analysis of treated rats revealed significantly reduced sperm cell concentration, live cell percentage, and motility index, and a significantly higher percentage of total sperm abnormalities, relative to controls. Plasma testosterone levels were significantly reduced as early as 14 days following the beginning of treatment, remaining significantly lower 21 days after treatment ceased. Male fertility was tested at the end of treatment and 60 days posttreatment. At both time points, the percentage of successful matings to untreated female rats was 50% that of controls.

Similarly, oral administration of cypermethrin to male rats at 3.8 and 7.7 mg/kg/day (El-Khalek et al. 1999) and fenvalerate at 20 or 100 mg/kg/day (Hassan et al. 1993) for 65 days resulted in reduced male reproductive organ weights and significantly altered sperm characteristics. Hassan et al. (1993) also found reduced percentages of pregnancies in untreated female rats that were mated with fenvalerate-treated males, while El-Khalek et al. (1999) observed significant decreases in plasma testosterone levels in cypermethrin-treated rats.

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.6 Developmental Effects

No reports were located regarding developmental effects in humans following oral exposure to pyrethrins or pyrethroids.

Standard tests for developmental effects in animals following oral exposure to pyrethrins or pyrethroids provide little indication that pyrethrins or pyrethroids might pose a significant developmental toxicity concern. However, more focused testing has revealed some persistent neurotoxic effects in animals exposed *in utero* and or via lactation.

Oral administration of pyrethrins (from pyrethrum extract) to female rats on gestation days 6–15 at doses in the range of 5–600 mg (total pyrethrins)/kg/day did not cause apparent developmental effects, even at doses in which maternal toxicity was observed (Schoenig 1995). However, high postimplantation loss was noted when pregnant rabbits were administered total pyrethrins at 600 mg/kg/day on gestation days 7–19 (Schoenig 1995). This dose level resulted in serious maternal toxicity (tremors, convulsions, and death). The World Health Organization (WHO 2001) reviewed the database for various pyrethroids and published a number of Environmental Health Criteria documents in which animal developmental toxicity studies (mostly unpublished or proprietary information from chemical organizations) provided little indication that pyrethroids might pose a developmental toxicity concern. The EPA evaluated a number of developmental toxicity studies (not currently available to ATSDR) that are briefly summarized in documents in which reference doses (RfDs) were derived for three Type I and seven Type II pyrethroids (IRIS 2001). These RfDs are presented in Table 8-1 of Chapter 8. Significant signs of developmental toxicity were not indicated in these studies. No serious signs of fetotoxicity or teratogenicity were observed in fetuses of rats administered deltamethrin at doses of 1, 2.5, or 5 mg/kg/day during gestation days 6 through 15, although the highest dose level resulted in the death of 4/20 treated dams (Bhaumik and Gupta 1990). Oral administration of cypermethrin to pregnant rats at 2, 4, or 8 mg/kg/day on gestation days 6–15 resulted in neither maternal toxicity nor significant incidences of fetotoxicity or teratogenicity (Gupta 1990). Abdel-Khalik et al. (1993) reported significant dose-dependent postimplantation loss and retarded growth in fetuses of rat dams administered deltamethrin at oral dose levels of 1, 2.5, or 5 mg/kg/day from gestation days 6–15. However, since treatment-related significantly increased placental weight was noted at all dose levels, the investigators considered the developmental effects to have resulted, at least in part, from compromised placental tissues in treated dams. Kavlock et al. (1979) found no significant treatment-related signs of fetotoxicity or teratogenicity in fetuses of rat or mouse dams administered deltamethrin during major stages of organogenesis at dose levels up to and including those eliciting overt signs of maternal toxicity (up to 12 and 5 mg/kg/day in rat and mouse dams, respectively). In addition, deltamethrin administration to rat dams from gestation day 7 through lactation day 15, at daily oral doses of 2.5 or 5.0 mg/kg, resulted in no sign of adverse effects in 6-week-old female offspring that were subjected to open field measurements of activity and exploration, although a dose-related depression in growth was observed during the period of lactation.

Recent testing has indicated that exposure to pyrethroids during neonatal stages of development may result in neurological effects first seen in adulthood (Ahlbom et al. 1994; Eriksson and Fredriksson 1991; Eriksson and Nordberg 1990; Talts et al. 1998a). Eriksson and Nordberg (1990) found treatment-related changes in muscarinic acetylcholine (MACh) receptor density within the cerebral cortex of male mice that had been administered bioallethrin or deltamethrin in daily oral doses of 0.7 mg/kg/day on days 10 through 16 postpartum. In a study used as the basis for derivation of an acute oral MRL for deltamethrin (Type II pyrethroid), Eriksson and Fredriksson (1991) administered bioallethrin or deltamethrin to male mice in daily oral doses of 0.7 mg/kg on days 10 through 16 postpartum. The mice were behaviorally tested 1 day after the cessation of treatment and again at 4 months of age, after which various brain areas were tested for MACh receptor density. No significant differences were observed in locomotion of 17-day-old mice, relative to controls. However, when examined at 4 months of age, both bioallethrin- and deltamethrin-treated mice exhibited significantly increased spontaneous locomotor behavior. Upon histological examination, bioallethrin treatment resulted in significantly decreased MACh receptor density in the cerebral cortex. A trend toward a decrease in MACh receptor density was observed in deltamethrin-treated mice. In a subsequent dose-response study of these effects in bioallethrin-treated mice, Eriksson and coworkers (Ahlbom et al. 1994) found significant dose-related increases in spontaneous locomotor behavior in 4-month-old adult mice that had been administered daily oral doses of bioallethrin on postpartum days 10 through 16 at dose levels of 0.21, 0.42, and 0.7 mg/kg/day, relative to controls. A dose-dependent increase in MACh receptor density within the cerebral cortex was observed in 17-day-old mice that had been administered 0.21–0.7 mg bioallethrin/kg/day. In treated mice examined as adults, MACh receptor density was decreased in a dose-dependent manner. In contrast to the findings in the 0.21–0.7 mg/kg dose groups, results in mice administered 42 mg bioallethrin/kg daily exhibited significant decreases in locomotion and total activity counts and no significant differences in densities of MACh receptor density. Underlying mechanisms responsible for the differences observed in low-dose groups (0.21–0.7 mg/kg) and mice in the 42 mg/kg dose group, a level approaching that which would be expected to result in overt clinical signs of neurotoxicity, could not be explained. Nevertheless, the low-dose findings served as the basis for derivation of an acute oral MRL for bioallethrin (Type I pyrethroid).

Malaviya et al. (1993) observed significant increases in the levels of dopamine and muscarinic receptors of striatal membrane in rat pups that had been exposed to fenvalerate or cypermethrin *in utero*. In this study, pregnant dams were administered 10 mg fenvalerate/kg or 15 mg cypermethrin/kg on gestation days 5 through 21. These effects were more pronounced in pups that continued to be exposed via their mothers throughout 3 weeks of postpartum lactation. Other significant treatment-related effects in the brain included increased levels of acetylcholinesterase and decreased activities of monoamine oxidase and Na^+- and K^+-ATPase from gestational exposure to fenvalerate, decreases in monoamine oxidase and acetylcholinesterase during lactation in fenvalerate-exposed pups, and decreases in acetylcholinesterase and Na^+- and K^+-ATPase during lactation in cypermethrin-exposed pups.

Moniz et al. (1990) demonstrated pyrethroid-induced disruption of avoidance learning (significantly decreased latency in avoidance to the dark area of a maze) in 97- and 104-day-old adult rats that had nursed from mothers exposed to cyhalothrin in the drinking water throughout the entire period of lactation at a level resulting in an estimated maternal cyhalothrin dose of 27 mg/kg/day. During the exposure period, no indication of neurotoxicity was seen in motor activity of dams or nursing pups.

Santoni and coworkers reported treatment-related increases in natural killer (NK) cell and antibody-dependent cytotoxic activity, impaired thymocyte function, and increased and decreased numbers of T cells in peripheral blood and spleen, respectively, in rats after their mothers had been orally administered cypermethrin during gestation at 50 mg/kg/day, a dose schedule that did not result in clinical signs of maternal toxicity (Santoni et al. 1997, 1998, 1999). In one phase of these studies, marked and long-lasting increases were noted in plasma adrenaline and noradrenaline concentrations of offspring (from treated dams) that were tested up to 90 days postpartum (Santoni et al. 1999).

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.7 Cancer

No reports were located regarding cancer in humans following oral exposure to pyrethrins or pyrethroids.

Pyrethrins and pyrethroids do not appear to be carcinogenic agents, as evidenced by the lack of carcinogenicity in animal studies and the generally negative results obtained in numerous tests for genotoxicity, albeit at generally low levels of exposure. Pyrethrum extract was not oncogenic in rats or mice chronically administered pyrethrum extract in the diet at total pyrethrin concentrations of up to 3,000 ppm (approximately 250 mg/kg/day for 2 years) or 5,000 ppm (approximately 850 mg/kg/day for 18 months), respectively (Schoenig 1995).

Ishmael and Litchfield (1988) performed a cancer bioassay in rats and mice administered permethrin in the diet. Rats were administered permethrin at concentrations of 500, 1,000, or 2,500 ppm for 2 years and mice received 250, 1,000, or 2,500 ppm for a lifetime. The estimated daily doses in high-dose rats were 91.5 and 103.8 mg/kg/day for males and females, respectively, based on body weight and food consumption values presented. Estimated doses to the high-dose mice were 295.1 and 348.1 mg/kg/day for males and females, respectively. There was no evidence for a carcinogenic effect in treated rats. The only statistically significant increase in incidences of tumors in mice was an elevation in benign lung tumor incidences (17/70 high-dose males vs 11/70 in controls) in males, but not females, of the 2,500-ppm exposure group. The authors did not consider this to indicate a carcinogenic effect.

The EPA evaluated a number of animal cancer bioassays (not currently available to ATSDR) that are briefly summarized in documents in which RfDs were derived for several Type I and Type II pyrethroids (IRIS 2001). Results of these studies did not indicate a carcinogenic effect for the pyrethroids evaluated. The World Health Organization (WHO 2001) reviewed the database for various pyrethroids and published a number of Environmental Health Criteria documents in which animal cancer bioassays (mostly proprietary information from chemical organizations) provided little indication that pyrethroids should be considered carcinogens. No indications of a carcinogenic effect were observed in other cancer bioassays of fenvalerate-treated rats (Parker et al. 1984a) and mice (Cabral and Galendo 1990; Parker et al. 1983).

3.2.3 Dermal Exposure

3.2.3.1 Death

Two case reports were located in which death was associated with allergic reactions to dog shampoo products containing pyrethrins (Wagner 2000; Wax and Hoffman 1994). The relative contributions of inhalation and dermal exposure routes were not addressed. No other reports were located regarding death in humans following dermal exposure to pyrethrins or pyrethroids.

Several studies designed to assess the lethality of pyrethrins and pyrethroids could not establish dermal LD_{50} values (exposure level resulting in death of 50% of the dosed animals), even when administered the highest concentrations possible for given pyrethrin- or pyrethroid-containing substances were administered (see Kavlock et al. 1979; Litchfield 1985; Schoenig 1995). However, El-Elaimy (1986) observed 100% mortality within 4 days among male rats exposed by daily dermal applications of cyfluthrin that resulted in daily doses of 1,845 or 2,460 mg cyfluthrin/kg/day. Rats receiving daily doses of 615 or 1,250 mg/kg/day survived a 7-day treatment period. Death was noted in 2/10 male mice within 48 hours following dermal application of 1,800 mg fenvalerate/kg (Mitchell et al. 1988). Acute dermal LD_{50} values for laboratory animals, listed by a secondary source (Metcalf 1995) for several pyrethroids, were considered to be >5,000 mg/kg, but dermal LD_{50} values for tefluthrin, cyhalothrin, and cyfluthrin were in the range of 148–696 mg/kg. However, primary sources for these values were not listed and could not be verified. Deaths in domestic cats have been associated with erroneous exposure to concentrated (45–65%) permethrin products designed to be used as flea treatment for dogs (Meyer 1999). The increased sensitivity of the cat to concentrated permethrin may be the result of less efficient hepatic glucuronidation (Whittem 1995), a second step in the metabolism of pyrethroids in mammalian systems. No other information was located regarding death in animals following dermal exposure to pyrethrins or pyrethroids.

3.2.3.2 Systemic Effects

No reliable reports were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects in humans or animals following dermal exposure to pyrethrins or pyrethroids.

Dermal Effects. Slight skin irritation was observed in workers in plants producing pyrethrum extract to be used as insecticide powders in an early study by McCord et al. (1921). Paresthesia (an abnormal cutaneous sensation sometimes described as tingling, burning, stinging, numbness, and/or itching) has been reported in individuals occupationally exposed to pyrethroids; however, paresthesia is generally considered to be a neurological effect, not a dermal effect (see Section 3.2.3.4). Reports were not located in which dermal exposure to pyrethrins or pyrethroids could be associated with other dermal effects in humans.

Animal studies indicate that dermal exposure to pyrethrins or pyrethroids may result in slight dermal irritation, but they do not elicit strongly positive responses in standard dermal sensitization tests (see, for example, DOD 1977; Litchfield 1985; Schoenig 1995).

Ocular Effects. No reliable reports were located regarding ocular effects in humans following dermal exposure to pyrethrins or pyrethroids. Some workers reported irritation of the eyes after dipping conifer seedlings into solutions containing fenvalerate or permethrin (Kolmodin-Hedman et al. 1982); however, control groups were not included in the survey.

Animal studies indicate that pyrethrins and pyrethroids may cause mild ocular irritation upon contact with the eye (see, for example, DOD 1977; Litchfield 1985; Schoenig 1995).

3.2.3.3 Immunological and Lymphoreticular Effects

A single case report was located in which a 47-year-old farmer developed a hypersensitive response that included a widespread dermal rash after dipping sheep in a solution, the active component of which was flumethrin (Box and Lee 1996). The relative contributions of dermal and inhalation exposure were not indicated in the report. See Section 3.2.1.3 for information regarding immunological effects in humans following exposures to pyrethrins or pyrethroids that were likely mixed (inhalation, dermal, and possibly oral).

No reports were located regarding immunological effects in animals following dermal exposure to pyrethrins or pyrethroids.

3.2.3.4 Neurological Effects

Paresthesia (an abnormal cutaneous sensation sometimes described as tingling, burning, stinging, numbness, and itching) has been widely reported among individuals occupationally exposed to pyrethroids (Flannigan and Tucker 1985; Flannigan et al. 1985b; Knox et al. 1984; LeQuesne and Maxwell 1980; Tucker and Flannigan 1983; see also Vijverberg and van den Bercken 1990 for a summary of available information on occupationally-induced paresthesia). This effect is considered to be the result of a direct effect on intracutaneous nerve endings following dermal exposure to pyrethroids (LeQuesne and Maxwell 1980; Wilks 2000). In a double-blind study of volunteers exposed to fenvalerate via application to the earlobe (0.081 mg/cm^2), the onset of cutaneous sensations occurred at 1 hour postapplication, peaked at 3–6 hours, and lasted approximately 24 hours (Knox et al. 1984). Sensations included numbness, itching, burning, tingling, and warmth. A similar time-course for paresthesia was noted among agricultural workers exposed during or shortly following the spraying of fenvalerate on field crops (Tucker and Flannigan 1983). Type I (permethrin) and Type II (cypermethrin, fenvalerate, and flucythrinate) pyrethroids have been shown to induce differing severity in paresthesia responses in volunteers exposed on separate days to each pyrethroid in doses of 0.13 mg/cm^2 (Flannigan and Tucker 1985). The mildest responses were elicited by permethrin. Both cypermethrin and fenvalerate induced significantly more severe responses than those of permethrin. Responses to cypermethrin were significantly more severe than those induced by the other three pyrethroids (see Section 3.5.2 for a discussion of mechanisms responsible for differences in toxicity among various pyrethroids).

Signs of mild acute pyrethroid poisoning include dizziness, headache, and nausea, in addition to paresthesia. These signs have been associated with acute occupational (inhalation and dermal) exposure to various pyrethroids during outdoor or indoor spraying (Chen et al. 1991; Moretto 1991; Shujie et al. 1988; Zhang et al. 1991). Based on measurements of pyrethroids deposited on gauze pads during spraying, estimates of dermal deposits on exposed skin ranged from 0.013 to 0.347 μg/cm^2 (Chen et al. 1991) and from <0.01 to 141.61 μg/cm^2 (Zhang et al. 1991). Although dermal exposure was considered to be the major source of exposure, inhalation exposure was also likely. Facial paresthesia, dizziness, fatigue, miliary red facial papules, and sniffles and sneezes were noted in subjects exposed to deltamethrin and fenvalerate while packaging the insecticides (He et al. 1988). Both inhalation and dermal exposures were likely, although increased toxicity during summer months was indication that dermal exposure may have been increased when greater areas of skin were exposed due to warmer weather. He et al. (1991) reported increased peripheral nerve excitability in individuals following 3 days of exposure to deltamethrin during spraying, in the absence of other clinical signs of acute pyrethroid poisoning. Higher levels of exposure to pyrethroids result in additional clinical signs such as listlessness, muscular fasciculations, and mild disturbance of consciousness, indicative of moderate acute pyrethroid poisoning (Chen et al. 1991; He et al. 1989). Even higher exposure levels may result in convulsive attacks and coma (severe acute pyrethroid poisoning), effects that may last for several weeks (He et al. 1989).

Limited information was available regarding neurological effects in animals following dermal exposure to pyrethrins or pyrethroids. El-Elaimy (1986) observed signs of pyrethroid poisoning (chewing, licking, and salivation) in groups of rats receiving daily dermal applications of cyfluthrin for up to 7 days. In this study, dose levels were 0, 615, 1,250, 1,845, and 2,460 mg cyfluthrin/kg/day. Pawing, whole body tremors, and choreoathetosis were noted at the two highest dose levels, which were also lethal. The description of the findings did not indicate whether clinical signs of neurotoxicity were seen at all dose levels. Significant increases were noted in grouped total activity and individual nonambulatory (but not ambulatory) activity of male mice observed for 4 hours following single dermal application of 300 mg permethrin/kg or $600 mg fenvalerate/kg (Mitchell et al. 1988). These effects were observed in the absence of typical clinical signs of pyrethroid-induced neurotoxicity. Guinea pigs responded to dermal applications of permethrin or fenvalerate by licking, rubbing, scratching, or biting the area of application (Cagen et al. 1984). These behavioral responses were indicative of paresthesia (considered to result from a direct action of pyrethroids on sensory nerve endings), since these responses were elicited in the absence of visible signs of dermal irritation.

3.2.3.5 Reproductive Effects

No reports were located regarding reproductive effects in humans or animals following dermal exposure to pyrethrins or pyrethroids.

3.2.3.6 Developmental Effects

No reports were located regarding developmental effects in humans following dermal exposure to pyrethrins or pyrethroids.

Available information regarding developmental effects in animals is limited to a single study in which 1 mL of a 0.018% solution of cyhalothrin was applied daily to the skin of pregnant rats throughout gestation (Gomes et al. 1991a). Assuming a mature dam body weight of 0.32 kg (EPA 1988a), the initial dermal dose to the dams was approximately 56 mg/kg/day. A control group was similarly treated with vehicle only. Relative to controls, treated pups exhibited delays in development of fur, ear and eye opening, and testes descent into the scrotum. At weaning and 90 days of age, the frequency of spontaneous locomotion and active avoidance responses did not differ significantly among treated and control groups of offspring. However, when tested as adults for motivational responses, the total number of head-dips in a hole-board test (an index of motivational state) was decreased in offspring of treated dams, relative to control offspring.

3.2.3.7 Cancer

No reports were located regarding cancer in humans or animals following dermal exposure to pyrethrins or pyrethroids.

3.3 GENOTOXICITY

Limited information regarding the genotoxicity of natural pyrethrins was located in the studies available for review. As shown in Table 3-2, natural pyrethrins, tested in the standard Ames test in various *Salmonella* strains and in *Escherichia coli* with or without metabolic activation gave negative results (Moriya et al. 1983).

Much more information has been generated regarding the genotoxic properties of both Type I and Type II pyrethroids. For example, administration of the Type I pyrethroids cismethrin (31 or 40 mg/kg) or bioresmethrin (1,000 mg/kg) to female Sprague-Dawley rats by gavage significantly increased the percentage of micronuclei in bone marrow (Hoellinger et al. 1987). In male and female CD-1 mice, intraperitoneal administration of a single dose of permethrin at up to 275 mg/kg failed to increase the percentage of micronuclei in bone marrow (ChruŇcielska and Kalhorn 1999). In a 28-day study in male Wistar rats, daily administration of permethrin (12.6, 50.3, or 125.7 mg/kg) by gavage significantly increased the number of chromosome aberrations in a dose-related manner (Institóris et al. 1999b). A commercial formulation of permethrin fed to the larva of *Drosophila* was mutagenic in the sex-linked recessive lethal mutation assay in *Drosophila*, affecting the DNA of both spermatogonia and

Table 3-2. Genotoxicity of Pyrethrins *In Vitro*

Species (test system)	Chemical	End point	With Activation	Without Activation	Reference
Prokaryotic organisms:					
Salmonella typhimurium (TA100, TA98, TA1535, TA1537, TA1538)	Pyrethrins	Gene mutation	–	–	Moriya et al. 1983
Escherichia coli (WP2 *hcr*)	Pyrethrins	Gene mutation	–	–	Moriya et al. 1983

– = negative result

spermatocytes (Kale et al. 1995). In contrast, in a study by Gupta et al. (1990), treating adult males resulted in no significant differences in frequencies of spontaneous mutations. The genotoxicity of Type I pyrethroids *in vivo* is summarized in Table 3-3.

Several Type II pyrethroids have been tested for genotoxicity in mammalian systems (mostly to rats and mice) following oral, parenteral, or dermal administration of the compounds (Table 3-4). Tests conducted with cypermethrin showed that doses $30 mg/kg administered intraperitoneally significantly increased the incidence of chromosomal aberrations and micronuclei in bone marrow and the percent of sperm with head abnormalities (Bhunya and Pati 1988). A dose of 50 mg/kg by gavage, but not dermally, also induced chromosomal aberrations in bone marrow (Bhunya and Pati 1988). Of the three assays used by these investigators, the sperm abnormality test was found to be the most sensitive and the micronucleus test the least sensitive. Other studies with higher doses of cypermethrin also have observed chromosomal aberrations in mouse bone marrow and spleen cells (Amer et al. 1993). Increased incidences of sister chromatid exchanges were also reported by Amer et al. (1993) in mouse bone marrow after an intraperitoneal dose of 180 mg cypermethrin/kg and by Chauhan et al. (1997) after a gavage dose of 32 mg/kg, but not 21.1 mg cypermethrin/kg. Experiments conducted with cypermethrin-dosed rats showed increased chromosomal aberrations in bone marrow after administration at 22.2 mg/kg/day for 28 days, but not 11.1 mg/kg/day (Institóris et al. 1999b). However, Nehéz et al. (2000), also in a 4-week gavage study, did not find increases in chromosomal aberrations in bone marrow from rats treated with up to 22 mg cypermethrin/kg/day. No significantly increased incidences of micronuclei were observed in rat bone marrow following acute treatment by gavage with 15 mg cypermethrin/kg (Hoellinger et al. 1987).

Studies of deltamethrin-dosed mice showed increased chromosomal aberrations and micronuclei in bone marrow cells, and sperm abnormalities following acute intraperitoneal treatment with $10 mg/kg (Bhunya and Pati 1990). Increased sister chromatid exchanges were detected after a single 20 mg/kg dose, but not 13.2 mg/kg or lower (Chauhan et al. 1997). A slight increase in dominant lethal mutation rate was observed in mice treated orally with 0.36, 0.72, or 1.08 mg deltamethrin/kg, but no dose-response was apparent (Shukla and Taneja 2000). In rats, acute intraperitoneal administration of deltamethrin at $5.6 mg/kg induced micronuclei in bone marrow cells (Agarwal et al. 1994), but gavage administration at up to 20 mg/kg did not (Hoellinger et al. 1987). This is consistent with other experiments conducted by Agarwal et al. (1994) in which intraperitoneal and subcutaneous administration of deltamethrin ($11.2 mg/kg) proved to be more efficient routes for inducing

Table 3-3. Genotoxicity of Type I Pyrethroids *In Vivo*

Species (test system)	Chemical	End point	Results	Reference
Eukaryotic organisms:				
Drosophila	Permethrin	Sex linked recessive lethal	+	Kale et al. 1995
Drosophila	Permethrin	Sex linked recessive lethal	–	Gupta et al. 1990
Mammalian cells:				
Rat bone marrow	Bioresmethrin	Micronuclei	+	Hoellinger et al. 1987
Rat bone marrow	Cismethrin	Micronuclei	+	Hoellinger et al. 1987
Rat bone marrow	Permethrin	Chromosomal aberrations	+	Institóris et al. 1999b
Rat bone marrow	Permethrin	Micronuclei	+	Hoellinger et al. 1987
Mouse bone marrow	Permethrin	Micronuclei	–	ChruÑcielska and Kalhorn 1999

– = negative result; + = positive result

Table 3-4. Genotoxicity of Type II Pyrethroids *In Vivo*

Species (test system)	Chemical	End point	Results	Reference
Eukaryotic organisms:				
Drosophila	Cypermethrin	Sex-linked recessive lethal	±	Batiste-Alentorn et al. 1986
Drosophila	Cypermethrin	Sex-chromosome loss	–	Batiste-Alentorn et al. 1986
Drosophila	Cypermethrin	Non-disjunction	–	Batiste-Alentorn et al. 1986
Drosophila	Supercyper-methrin	Sex-linked recessive lethal	–	Miadoková et al. 1992
Drosophila	Supercyper-methrin	Sex-chromosome loss, non-disjunction, frequency of deletion	–	Miadoková et al. 1992
Mammalian systems:				
Rat bone marrow	Cypermethrin	Chromosomal aberrations	+	Institóris et al. 1999b
Rat bone marrow	Cypermethrin	Chromosomal aberrations	–	Nehéz et al. 2000
Mouse bone marrow	Cypermethrin	Chromosomal aberrations	+, –	Bhunya and Pati 1988
Mouse bone marrow	Cypermethrin	Chromosomal aberrations	+	Amer et al. 1993
Mouse spleen cells	Cypermethrin	Chromosomal aberrations	+	Amer et al. 1993
Mouse bone marrow	Cypermethrin	Sister chromatid exchange	+	Chauhan et al. 1997
Mouse bone marrow	Cypermethrin	Sister chromatid exchange	+	Amer et al. 1993
Rat bone marrow	Cypermethrin	Micronuclei	–	Hoellinger et al. 1987
Mouse bone marrow	Cypermethrin	Micronuclei	+	Bhunya and Pati 1988
Mouse sperm	Cypermethrin	Cellular abnormalities	+	Bhunya and Pati 1988
Rat bone marrow	Deltamethrin	Chromosomal aberrations	+	Agarwal et al. 1994
Mouse bone marrow	Deltamethrin	Chromosomal aberrations	+	Bhunya and Pati 1990
Mouse bone marrow	Deltamethrin	Chromosomal aberrations	–	Poláková and Vargová 1983
Mouse bone marrow	Deltamethrin	Sister chromatid exchange	+	Chauhan et al. 1997
Rat bone marrow	Deltamethrin	Micronuclei	+	Agarwal et al. 1994
Rat bone marrow	Deltamethrin	Micronuclei	–	Hoellinger et al. 1987
Mouse bone marrow	Deltamethrin	Micronuclei	+	Bhunya and Pati 1990
Mouse bone marrow	Deltamethrin	Micronuclei	+	Gandhi et al. 1995
Rat testes	Deltamethrin	DNA fragmentation	+	El-Gohary et al. 1999
Mouse sperm	Deltamethrin	Cellular abnormalities	+	Bhunya and Pati 1990
Mouse	Deltamethrin	Dominant lethal mutations	±	Shukla and Taneja 2000

Table 3-4. Genotoxicity of Type II Pyrethroids *In Vivo (continued)*

Species (test system)	Chemical	End point	Results	Reference
Rat bone marrow	Fenpropathrin (Meothrin)	Micronuclei	+	Oraby 1997
Mouse bone marrow	Fenpropathrin	Micronuclei	–	Ryu et al. 1996
Rat bone marrow	Fenvalerate	Chromosomal aberrations	+	Chatterjee et al. 1982
Mouse bone marrow	Fenvalerate	Chromosomal aberrations	+	Ghosh et al. 1992
Mouse bone marrow	Fenvalerate	Chromosomal aberrations	+	Pati and Bhunya 1989
Mouse sperm	Fenvalerate	Cellular abnormalities	+	Pati and Bhunya 1989
Mouse bone marrow	Flumethrin	Chromosomal aberrations	+, –	Nakano et al. 1996
Mouse bone marrow	Flumethrin	Micronuclei	+, –	Nakano et al. 1996

– = negative result; + = positive result; ± = weak positive result; +, – = both positive and negative results; DNA = deoxyribonucleic acid chromosomal aberrations than gavage. Deltamethrin also was shown to induce DNA fragmentation in sections of rat testes following intraperitoneal administration of 1 mg/kg/day (only level tested) for 21 days (El-Gohary et al. 1999).

In mice dosed intraperitoneally, fenvalerate induced chromosomal aberrations in bone marrow cells at $32.5 mg/kg (Ghosh et al. 1992; Pati and Bhunya 1989), micronuclei at 150 mg/kg, and sperm abnormalities at 100 mg/kg (Pati and Bhunya 1989). Fenvalerate also induced chromosomal aberrations in rat bone marrow cells following gavage dosing at $50 mg/kg/day for 21 days (Chatterjee et al. 1982). Studies conducted with flumethrin in mice showed induction of chromosomal aberrations in bone marrow cells after a single dermal application of 5,325 mg/kg to a shaved area or a single intraperitoneal injection of 2,083 mg/kg, but not after repeated intraperitoneal injections of 128 mg/kg (Nakano et al. 1996). In contrast, micronuclei frequency was not significantly elevated after a single dermal dose of 5,325 mg/kg, but was increased after repeated intraperitoneal doses of 128 mg/kg (Nakano et al. 1996). Additional studies found no significant increase in chromosomal aberrations in mouse bone marrow following a single gavage administration of deltamethrin by gavage at up to 6.8 mg/kg (Poláková and Vargová 1983) or of micronuclei after an intraperitoneal dose of up to 105 mg fenpropathrin/kg (Ryu et al. 1996). However, 14 daily doses of fenpropathrin by gavage at $0.074 mg/kg/day of increased the frequency of micronuclei in rat bone marrow (Oraby 1997); a dose of 0.0074 mg/kg/day was without significant effect.

A limited number of studies of Type II pyrethroids in *Drosophila* show mostly nonmutagenic results under the experimental conditions of the tests. Batiste-Alentorn et al. (1986) showed a small but significant increase in the frequency of sex-linked recessive lethal mutations after adult ingestion or larval feeding of cypermethrin. However, there were no significant increases in the frequency of sex-chromosome loss or nondisjunction. Similar negative results were reported by Miadoková et al. (1992).

Many *in vitro* studies have also been conducted on both Type I and Type II pyrethroids (Tables 3-5 and 3-6). Many papers investigated gene mutations in various *Salmonella* strains both with and without metabolic activation and, for the most part, the results did not indicate a mutagenic response. In yeast, results were inconsistent, although there was some evidence of mutations of mitochondrial DNA, particularly when commercial formulations were tested, but not when only the active ingredient was tested (ChruÑcielska et al. 1999).

Table 3-5. Genotoxicity of Type I Pyrethroids *In Vitro*

Species (test system)	Chemical	End point	With Activation	Without Activation	Reference
Prokaryotic organisms:					
Escherichia coli (WP2 *her*)	Allethrin	Gene mutation		–[a]	Moriya et al. 1983
Salmonella typhimurium (TA98, JK1)	Allethrin	Gene mutation		–[b]	Hour et al. 1998
S. typhimurium (JK3, JK947)	Allethrin	Gene mutation		+[b]	Hour et al. 1998
S. typhimurium (TA98, TA1535, TA1537, TA1538)	Allethrin	Gene mutation		–[a]	Moriya et al. 1983
S. typhimurium (TA100)	Allethrin	Gene mutation	+	+	Moriya et al. 1983
S. typhimurium (TA97, TA100, TA104)	Allethrin	Gene mutation	+	–	Herrera and Laborda 1988
S. typhimurium (TA98, TA1535, TA1538, TA1537)	Allethrin	Gene mutation	–	–	Herrera and Laborda 1988
S. typhimurium (TA98, TA100)	Bioresmethrin	Gene mutation	–	–	Pluijmen et al. 1984
S. typhimurium (TA98, T100)	Cismethrin	Gene mutation	–	–	Pluijmen et al. 1984
E. coli (WP2 *her*)	Permethrin	Gene mutation		–[a]	Moriya et al. 1983
S. typhimurium (TA98, TA100)	Permethrin	Gene mutation	–	–	Pluijmen et al. 1984
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	Permethrin	Gene mutation		–[a]	Moriya et al. 1983
S. typhimurium (TA98, TA100)	Permethrin	Gene mutation	–		Bartsch et al. 1980
S. typhimurium (TA97, TA98, TA100, TA104, TA1535, TA1537, TA1538)	Permethrin	Gene mutation	–	–	Herrera and Laborda 1988
S. typhimurium (TA98, TA100)	Resmethrin	Gene mutation	–	–	Pluijmen et al. 1984
S. typhimurium (TA97, TA98, TA100, TA104, TA1535, TA1537, TA1538)	Resmethrin	Gene mutation	–	–	Herrera and Laborda 1988

Table 3-5. Genotoxicity of Type I Pyrethroids *In Vitro (continued)*

Species (test system)	Chemical	End point	With Activation	Without Activation	Reference
Eukaryotic organisms:					
Yeast (Strain A and HB)	Ambush 25EC (Permethrin)	Mitochondrial mutation		+	ChruÑcielska et al. 1999
Yeast (Strain A and HB)	Permethrin	Mitochondrial mutation		–	ChruÑcielska et al. 1999
Mammalian cells:					
Chinese hamster ovary cells	Bioresmethrin	Gene mutation		–	Pluijmen et al. 1984
Chinese hamster ovary cells	Cismethrin	Gene mutation		–	Pluijmen et al. 1984
Chinese hamster ovary cells	Permethrin	Chromosomal aberrations		+	Barrueco et al. 1994
Human lymphocytes	Permethrin	Chromosomal aberrations	–	+	Barrueco et al. 1992
Human lymphocytes	Permethrin	Chromosomal aberrations		+	Barrueco et al. 1994
Human lymphocytes	Permethrin	Sister chromatid exchange	±	±	Barrueco et al. 1992
Human lymphocytes	Permethrin	Micronuclei		+	Barrueco et al. 1992
Human lymphocytes	Permethrin	Micronuclei		–	Surrallés et al. 1995
Human whole blood	Permethrin	Micronuclei		–	Surrallés et al. 1995
Chinese hamster ovary cells	Permethrin	Gene mutation		–	Pluijmen et al. 1984
Chinese hamster ovary cells	Resmethrin	Gene mutation		–	Pluijmen et al. 1984

[a]Not clear whether tests were performed with or without activation.
[b]Tests assumed to be performed without activation because use of activation was not discussed in the study.

– = negative result; + = positive result; ± = weak positive result

Table 3-6. Genotoxicity of Type II Pyrethroids *In Vitro*

Species (test system)	Chemical	End point	With Activation	Without Activation	Reference
Prokaryotic organisms:					
Salmonella typhimurium (TA98, 100)	Cypermethrin	Gene mutation	–	–	Pluijmen et al. 1984
S. typhimurium (TA98)	Deltamethrin	Gene mutation	–		Bartsch et al. 1980
S. typhimurium (TA100)	Deltamethrin	Gene mutation	–	+	Bartsch et al. 1980
S. typhimurium (TA98, TA100)	Deltamethrin	Gene mutation	–	–	Pluijmen et al. 1984
S. typhimurium (TA98, TA100, TA1535, TA1537)	Fenpropathrin	Gene mutation	–	–	Ryu et al. 1996
S. typhimurium (TA98, TA100)	Fenvalerate	Gene mutation	–	–	Pluijmen et al. 1984
S. typhimurium (TA97, TA98, TA100, TA1535, TA1538)	Supercyper-methrin	Gene mutation	–	–	Miadoková et al. 1991
Eukaryotic organisms:					
Yeast (Strains A and HB)	Cypermethrin	Mitochondrial mutation		–	ChruÑcielska et al. 1999
Yeast (Strains A and HB)	Fastac 10EC (10% alpha-cypermethrin)	Mitochondrial mutation		±	ChruÑcielska et al. 1999
Yeast (Strains A and HB)	Deltamethrin	Mitochondrial mutation		–	ChruÑcielska et al. 1999
Yeast (Strains A and HB)	Decis 2.5EC (2.5% delta-methrin)	Mitochondrial mutation		+	ChruÑcielska et al. 1999
Yeast (Strains A and HB)	Karate 025EC (25 g/L lambda-cyhalothrin)	Mitochondrial mutation		+	ChruÑcielska et al. 1999
Yeast Strain D7	Supercyper-methrin	Mitotic cross-over		± or –	Vl…ková 1991
Yeast Strain D7	Supercyper-methrin	Conversion at the tryptophan locus		± or –	Vl…ková 1991
Yeast Strain D7	Supercyper-methrin	Conversion at the tryptophan locus		+	Miadoková et al. 1992
Yeast Strain D7	Supercyper-methrin	Gene reversion mutations		+	Vl…ková 1991

Table 3-6. Genotoxicity of Type II Pyrethroids *In Vitro (continued)*

Species (test system)	Chemical	End point	With Activation	Without Activation	Reference
Yeast Strain D7	Supercyper-methrin	Point mutations at isoleucine locus		+	Miadoková et al. 1992
Mammalian systems:					
Human lymphocytes	Cypermethrin	Sister chromatid exchange		–	Puig et al. 1989
Human lymphocytes	Cypermethrin	Micronuclei		±	Surrallés et al. 1995
Human whole blood	Cypermethrin	Micronuclei		±	Surrallés et al. 1995
Mouse spleen cells	Cypermethrin	Chromosomal aberrations		+	Amer et al. 1993
Mouse spleen cells	Cypermethrin	Sister chromatid exchange		+	Amer et al. 1993
Chinese hamster ovary cells	Cypermethrin	Gene mutation		–	Pluijmen et al. 1984
Human lymphocytes	Deltamethrin	Sister chromatid exchange		±	Dolara et al. 1992
Human lymphocytes	Deltamethrin	Sister chromatid exchange	–	–	Villarini et al. 1998
Human lymphocytes	Deltamethrin	Micronuclei		±	Surrallés et al. 1995
Human lymphocytes	Deltamethrin	Micronuclei	–	–	Villarini et al. 1998
Human lymphocytes	Deltamethrin	DNA damage	+	±	Villarini et al. 1998
Human whole blood	Deltamethrin	Micronuclei		±	Surrallés et al. 1995
Chinese hamster ovary cells	Deltamethrin	Gene mutation		–	Pluijmen et al. 1984
Chinese hamster lung fibroblasts	Fenpropathrin	Chromosomal aberrations	–	–	Ryu et al. 1996
Human lymphocytes	Fenpropathrin	Micronuclei		±	Surrallés et al. 1995
Human whole blood	Fenpropathrin	Micronuclei		±	Surrallés et al. 1995
Human lymphocytes	Fenvalerate	Chromosomal aberrations		+	Puig et al. 1989
Chinese hamster ovary cells	Fenvalerate	Chromosomal aberrations	+	–	Caballo et al. 1992
Chinese hamster ovary cells	Fenvalerate	Sister chromatid exchange	+	+	Caballo et al. 1992
Human lymphocytes	Fenvalerate	Micronuclei		–	Surrallés et al. 1995
Human whole blood	Fenvalerate	Micronuclei		–	Surrallés et al. 1995
Human lymphocytes	Fenvalerate	C–mitosis induction		+	Carbonell et al. 1989

Table 3-6. Genotoxicity of Type II Pyrethroids *In Vitro (continued)*

Species (test system)	Chemical	End point	With Activation	Without Activation	Reference
Chinese hamster ovary cells	Fenvalerate	Gene mutation		–	Pluijmen et al. 1984
Pig lymphocytes	Supermethrin	Chromosomal aberrations		+	Dianovský and Šiviková 1997
Cattle lymphocytes	Supermethrin	Chromosomal aberrations		+	Dianovský and Šiviková 1997
Pig lymphocytes	Supermethrin	Sister chromatid exchange		–	Dianovský and Šiviková 1997
Cattle lymphocytes	Supermethrin	Sister chromatid exchange		±	Dianovský and Šiviková 1997
Syrian hamster embryo cells	Supercyper-methrin	Morphological transformation		+	SlameÁová et al. 1992
BHK21 (baby hamster kidney cells)	Supercyper-methrin	Anchorage independent growth	+	+	SlameÁová et al. 1992

– = negative result; + = positive result; ± = weak positive result; DNA = deoxyribonucleic acid

In vitro experiments in mammalian cells show a slightly greater percentage of mutagenic effects than the bacteria and yeast studies (Tables 3-5 and 3-6). Investigations of human, pig, and cattle lymphocytes, Chinese and Syrian hamster cells, and mouse spleen cells were positive for several genetic end points. Chromosomal aberrations, sister chromatid exchange, increased micronuclei, DNA damage, C-mitosis induction, and other damage were all observed. However, as with the bacteria studies, no consistent pattern was seen that could relate genotoxicity to the presence or absence of metabolic activation of the pyrethroids by liver cells or enzymes.

3.4 TOXICOKINETICS

Pyrethroids have been classified into two major categories, Type I or Type II, based on distinct toxicological mechanisms (see Section 3.5.2 for details regarding the classification of pyrethroids). Although synthetic pyrethroids are all derivatives of the natural pyrethrins, they exhibit a wide structural diversity and some differences in their toxicokinetics. The differences are most apparent in the metabolism of individual pyrethroid compounds (see Section 3.4.3). Thus, while generalizations are made in the profile regarding the toxicokinetics of the major pyrethroid classes and the basis for these generalizations is provided, the reader is cautioned about applying these generalizations too strictly to specific pyrethroid compounds, even within a class. Relevant literature regarding the toxicokinetics of specific pyrethroid compounds is cited where appropriate to this review, and the reader is encouraged to pursue such literature if information is needed regarding specific pyrethroid compounds.

Results of studies of volunteers and laboratory animals indicate that Type I and Type II pyrethroid compounds are absorbed from the gastrointestinal tract following oral exposure. Absorption is incomplete, with minimum estimates for absorption between 40 and 60% of an orally or intragastrically administered dose. However, first-pass metabolism may contribute significantly to under-estimation of the absorption of pyrethroids. Pyrethroids are rapidly absorbed in humans following inhalation exposure, but no estimates are available regarding how much of an inhaled dose is absorbed. Only small amounts (<2% of the applied dose) of pyrethroids are absorbed following dermal exposure and the rate of absorption from this route is much slower than by the oral or inhaled routes. Pyrethroids may be stored in skin and then slowly released into the systemic circulation. Distribution of pyrethroids has not been well studied in humans and most of the available information is based on the results of studies in animals. Following absorption, pyrethroids are widely and rapidly distributed to most tissues, particularly to tissues with a high lipid content, and are concentrated in central and peripheral nervous tissues. Although there is little information on the metabolism of pyrethroids in humans, metabolism of pyrethroids has been extensively studied in animal models. The major metabolic pathways for pyrethroids are hydrolysis of the central ester bond, oxidative attacks at several sites, and conjugation reactions, to produce a complex array of primary and secondary water-soluble metabolites that undergo urinary excretion. Information on the specific enzymes involved in metabolism of pyrethroid compounds is limited, but appears to involve nonspecific microsomal carboxyesterases and microsomal mixed function oxidases, which are located in nearly all tissue types, with particularly high activities in the liver. Since microsomal enzymes play an important role in the metabolism of pyrethroids, it is expected that many tissue types are potentially capable of rapidly metabolizing these compounds. Elimination and excretion of pyrethroids in humans has not been extensively studied. Elimination appears to follow first-order kinetics, with elimination half-times in humans ranging from 6.4 to 16.5 hours, depending upon the specific pyrethroid and exposure route studied. For most pyrethroids, elimination is nearly complete within 5 days of exposure, although certain isomers can persist in the body for a longer period of time. Pyrethroids have been shown to undergo urinary and fecal excretion in humans, but other routes of excretion, such as exhalation of volatile products, have not been studied. In animals, Type I and Type II pyrethroids undergo urinary, fecal, and biliary excretion, with urinary and fecal excretion as the primary routes; small quantities are also excreted in milk. Pyrethroids do not appear to be excreted as parent compounds via expired air of animals.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Several studies demonstrate absorption of Type I and Type II pyrethroids following occupational exposure through identification of pyrethroid metabolites in urine (Aprea et al. 1997; Chester et al. 1987, 1992; Kühn et al. 1999; Leng et al. 1996; 1997b). In some cases, plasma levels of pyrethroids were below the limits of detection (5 μg/L) (Leng et al. 1997a, 1997b). Absorption of cyfluthrin in workers was confirmed by measurement of plasma cyfluthrin levels, although estimates of total exposure levels of cyfluthrin in these workers were not available (Leng and Lewalter 1999). It appears that pyrethroids are rapidly absorbed following inhalation, based on the appearance of urinary metabolites within 30 minutes of exposure (Leng et al. 1997a). In this study, an increase in the amount of urinary metabolites correlated with increasing exposure levels, indicating that absorption by the inhalatory route is not capacity-limited, at least over the range of exposures studied (10–160 mg/m^3). However, occupational exposure of humans to pyrethroids may include inhalation, oral, and/or dermal routes. Studies providing estimates for total absorption of pyrethroids following inhalation or occupational exposure were not identified.

No information was located regarding absorption of pyrethroids following inhalation exposure in animals.

3.4.1.2 Oral Exposure

Available information regarding oral exposure of humans indicates that both Type I and Type II pyrethroids are absorbed from the gastrointestinal tract. A 59-year-old male attempted suicide by drinking approximately 600 mL of 20% permethrin emulsion (143 grams) (Gotoh et al. 1998). The emulsion contained a mix of cis and trans isomers (43.5% cis and 56.5% trans). Maximal plasma concentrations of permethrin occurred 3–4 hours after ingestion. Both isomers were detected in plasma, indicating that both cis and trans isomers of permethrin are absorbed following oral administration. It is not possible to determine what fraction of the administered dose was absorbed in this patient. Oral exposure of a single volunteer demonstrated absorption of cyfluthrin by measurement of cyfluthrin metabolites in the urine, with an estimated minimum oral absorption of 40%, based on recovery of urinary cyfluthrin metabolites (Leng et al. 1997b). Similar results were observed in male volunteers exposed to cypermethrin, with absorption estimates ranging from 36 to 63% of the administered dose (Eadsforth and Baldwin 1983; Eadsforth et al. 1988; Woollen et al. 1992). Estimates of absorption following oral exposure to pyrethroids may be low, however, since they are based on the appearance of metabolites in the urine and do not consider other routes of excretion, such as biliary excretion.

Observations in humans are supported by the results of animal studies. In several mammalian species, absorption of Type I pyrethroids following oral administration has been demonstrated by the presence of pyrethroid compounds in plasma, urine, and milk (Anadón et al. 1991b; Elliott et al. 1976; Gaughan et al. 1977, 1978; Hunt and Gilbert 1977; Ohsawa and Casida 1980; Tomigahara et al. 1994a, 1994b; Ueda et al. 1975a, 1975b). Following oral administration of a single dose of permethrin to rats, peak plasma levels of permethrin occurred 3–4 hours after ingestion, with an estimated total absorption of approximately 60% of the administered dose (Anadón et al. 1991b). In cows administered resmethrin orally, 43% of the administered dose was excreted in the urine as resmethrin metabolites, indicating a minimum absorption of 43% of the administered dose (Ridlen et al. 1984). Absorption of several Type II pyrethroids following oral administration has been demonstrated by the presence of pyrethroid compounds in plasma, urine, and milk (Anadón et al. 1996; Quistad and Selim 1983; Quistad et al. 1982, 1983). In Rhesus monkeys exposed to oral doses of ^{14}C-fluvalinate, peak plasma levels were observed 2–3 hours after administration, with 37% of the administered dose eliminated in the urine as metabolites (Quistad and Selim 1983).

Differences in the rate and extent of absorption in young versus older rats was demonstrated in one study of rats administered ^{14}C-fluvalinate by gavage (Quistad et al. 1983). In younger rats (7 weeks old), peak plasma levels of ^{14}C occurred at 7 hours, compared to 14 hours in older rats. However, lower plasma ^{14}C levels were observed in younger compared to older rats; thus, it is not clear whether fractional absorption was lower or higher in the younger rats. No information was located that could serve as a basis for predicting the effects of age on absorption of pyrethroids from the human gastrointestinal tract.

No information was located regarding possible sex-related differences in absorption of ingested pyrethroids in humans or animals.

3.4.1.3 Dermal Exposure

Limited information is available regarding absorption of Type I or Type II pyrethroids following dermal exposure in humans. Following dermal application of permethrin to patients for treatment of scabies, the estimated absorption of permethrin was 0.5% of the applied dose, based upon the urinary excretion of permethrin metabolites (van der Rhee et al. 1989). Urinary excretion of metabolites persisted for 7–10 days following a single dermal application, suggesting that pyrethroids may be stored in skin and slowly released into the systemic circulation. A study using an *in vitro* preparation of human skin indicated that only a small fraction (approximately 0.7%) of a topically applied dose of permethrin fully penetrated the skin after a single 48-hour exposure, with small amounts of permethrin identified in the epidermal and dermal layers (Franz et al. 1996). Two studies evaluated the absorption of cypermethrin following dermal application of a single dose to volunteers (Eadsforth et al. 1988; Woollen et al. 1992). Based upon the recovery of urinary metabolites of cypermethrin, it was estimated that 0.3–1.8% of the applied dose was absorbed. Peak urinary excretion of metabolites was observed between 14 and 36 hours after application. This is in contrast to observations following oral exposure of cypermethrin in humans in which the urinary excretion rate of metabolites was highest during the first 24 hours after dosing (Woollen et al. 1992).

Limited animal data are available regarding absorption of Type I or Type II pyrethroids following dermal exposure. Results of one study in rats are consistent with findings in humans; approximately 0.7% of a dermal application of fluvalinate was absorbed (Quistad et al. 1983). A single study indicates that fenvalerate is absorbed more quickly following dermal exposure to goats compared with other mammalian species, with peak plasma concentrations reached 2 hours after dosing (Mandal et al. 1996). The total percutaneous absorption of fenvalerate was not determined in that study. Percutaneous absorption of permethrin was demonstrated in guinea pigs *in vivo* following a single dermal application (Franz et al. 1996). In this study, absorption was found to be 20-fold greater than that measured in a preparation of human skin. The percutaneous absorption of permethrin in rats, as measured by recovery of ^{14}C in urine and feces, was estimated to be 46% of the applied dose (Shah et al. 1987). This finding is not consistent with lower estimates from other studies in humans and animals and may be attributed to lack of restraint of the animals, allowing for oral exposure from licking of the application site. However, insufficient information is provided in the report to confirm this possibility. In this same study, there was no difference in the absorption of young (33 days) versus adult rats exposed to a single dermal application of permethrin.

No additional information was located regarding sex- or age-related differences in absorption of pyrethroids following dermal exposure in humans or animals. There is no obvious structural basis for predicting substantial differences in the percutaneous absorption of Type I and Type II compounds in humans.

3.4.2 Distribution

No information is available regarding the distribution of Type I and Type II pyrethroid compounds or pyrethroid metabolites in humans, except for information regarding the distribution of pyrethroids and pyrethroid metabolites into excretory compartments. Given the lipophilic nature of pyrethroids, it is expected that, in humans, they are widely distributed and undergo rapid distribution to tissues with a high lipid content, including fat and central and peripheral nervous tissues. Based upon observations of central and peripheral nervous system toxicity in humans exposed to pyrethroid compounds, it is apparent that distribution of pyrethroids to these tissues occurs (Aldridge 1990; Casida et al. 1983; Vijverberg and van den Bercken 1990). Since pyrethroid metabolites are less lipid soluble than the parent compounds, it is expected that distribution of metabolites to central and peripheral nervous tissues would be decreased compared to that of the parent compounds. Studies in several mammalian species confirm that pyrethroids are widely and rapidly distributed to many tissues, including liver and kidney, and are concentrated in central and peripheral nervous tissues. In pregnant and lactating animals, pyrethroids are distributed into milk. Although animal studies of placental transfer of pyrethroids indicate that pyrethroids do not cross the placenta in substantial amounts or accumulate in the fetus (Kaneko et al. 1984b; Quistad et al. 1982; Shiba et al. 1990), other animal studies indicate that *in utero* exposure to pyrethroids may result in persistent effects on neurotransmitters (Malaviya et al. 1993; Santoni et al. 1999) and on the immune system (Santoni et al. 1997, 1998, 1999). Interpretation of results obtained from many of the distribution studies in animals is limited by the study design; the distribution of pyrethroids was typically evaluated in tissues collected from animals after most of the chemical had been excreted from the body (1–8 days after treatment with the last dose).

3.4.2.1 Inhalation Exposure

No information was located regarding the distribution of pyrethroids in humans or animals following inhalation exposure.

3.4.2.2 Oral Exposure

Limited information is available on the distribution of Type I or Type II pyrethroids in humans following oral exposure, and most of the available information describes the distribution of pyrethroids and pyrethroid metabolites into excretory compartments (reviewed in Section 3.4.3.2). Based on the results of a study in which plasma permethrin concentrations were measured in an adult male who ingested permethrin in a suicide attempt, permethrin appears to follow a two-compartment model, with distribution half-times for the trans and cis compounds of 5.08 and 4.82 hours, respectively (Gotoh at el. 1998). One study that investigated the elimination of ^{14}C-deltamethrin in volunteers following oral administration showed that small amounts of deltamethrin or its metabolites were distributed to saliva (Stockis et al. 1985). In this same study, evaluation of the distribution of ^{14}C in plasma indicated that approximately 25% of the plasma ^{14}C was associated with red blood cells.

In rats, permethrin was rapidly distributed to nervous tissues after administration of a single oral dose, with a distribution half-time of 4.85 hours (Anadón et al. 1991b). Plasma levels of permethrin exhibited a bi-phasic decline, which can be represented by a two-compartment model with a rapid distribution phase. Based on a large apparent volume of distribution, it appears that permethrin is distributed in both extracellular and intracellular fluids, indicating that pyrethroids can easily cross cell membranes. Permethrin concentrations in nervous tissue were higher than those measured in plasma, indicating that permethrin is concentrated in nerve tissue relative to plasma. Concentrations in nerve tissue were highest in the sciatic nerve, followed by (in decreasing order) hypothalamus, frontal cortex, hippocampus, caudate putamen, cerebellum, and medulla oblongata. Peak concentrations were observed to occur within 4 hours of dosing in both nerve tissue and plasma. Permethrin was also distributed to the liver, with peak concentrations observed within 4 hours of dosing. Concentrations of permethrin metabolites (*m*-phenoxy-benzyl alcohol and *m*-phenoxybenzoic acid) in nerve tissues were lower than those observed for the parent compound. Although it is not possible to determine if the permethrin metabolites entered the nerve tissue from blood or if permethrin was metabolized to its metabolites in nerve tissue, distribution of the more lipid soluble parent compounds into nerve tissue is considered more likely (Anadón et al. 1991a, 1991b). ^{14}C-permethrin or its metabolites are also rapidly distributed to the kidney following oral administration to rats, with levels of ^{14}C in the kidney peaking approximately 4 hours after dosing (Miyamoto et al. 1968). Studies in lactating cows indicate that very low levels of Type I pyrethroids (e.g., <0.5% of the administered dose) are distributed into milk (Gaughan et al. 1978; Ridlen et al. 1984). Following oral exposure, permethrin or its metabolites have also been detected in fat of cows and rats up to12 days after dosing (Gaughan et al. 1977, 1978).

Fluvalinate was widely distributed in rats following oral exposure to ^{14}C-fluvalinate, based on detection of small amounts of ^{14}C in nearly all tissue types (Ruzo et al. 1978). However, interpretation of these results must be made with caution, since tissue levels of ^{14}C were measured in animals that had been sacrificed 8 days after oral dosing and nearly all of the ^{14}C had been eliminated from the body by that time. In rats, deltamethrin was rapidly distributed to nerve tissues after administration of a single oral dose, with a distribution half-time of 2.1 hours (Anadón et al. 1996). Plasma levels of deltamethrin exhibited a bi-phasic decline, which can be represented by a two-compartment model with a rapid distribution phase. Deltamethrin concentrations in nerve tissue were higher than those measured in plasma, indicating that deltamethrin is concentrated in nervous tissue relative to plasma. Concentrations in nerve tissue were highest in the hypothalamus, followed by (in decreasing order) hippocampus, cerebellum, frontal cortex, caudate putamen, and medulla oblongata, with peak concentrations occurring between 4 and 6 hours after oral administration. Similar distribution was observed for the 4-OH-metabolite of deltamethrin but, in general, the concentrations of metabolite measured in each tissue were less than those measured for the parent compound. It is not possible to determine if the metabolite entered the nervous tissue from blood or if deltamethrin was metabolized to the 4-OH-metabolite by nervous tissue. However, distribution of the more lipid soluble parent compounds into nerve tissue is considered more likely due to the lower lipid solubility of the metabolites (Anadón et al. 1996). Deltamethrin and its 4-OH metabolite were also detected in vas deferens and anococcygeus muscle at concentrations that were greater than plasma but less than those observed in nervous tissue (Anadón et al. 1996). Residual amounts of pyrethroids have been measured in fat several days after oral exposure to lambs and cows (Quistad et al. 1982; Wszolek et al. 1981a, 1981b). Studies in lactating cows indicate that Type II pyrethroids are rapidly distributed into milk after exposure to a single oral dose, but that only small amounts of the total dose are distributed to milk (0.4–0.9% of the administered dose) (Quistad et al. 1982; Wszolek et al. 1980). Pyrethroids do not appear to cross the placenta in substantial amounts or accumulate in the fetus of animals, as evidenced by the results of dosing of pregnant rats and a single cow. Measurements of radioactivity in fetuses of rats administered radiolabeled pyrethroids indicated that <0.004% of the administered dose of the Type I pyrethroid, tetramethrin, was recovered in the fetus (Kaneko et al. 1984b). Recovered activity from radiolabeled fenvalerate (a Type II pyrethroid) was <0.07% (Shiba et al. 1990). Eight days after a pregnant cow was given a single a single dose of ^{14}C-fluvalinate, only trace amounts of ^{14}C were detected in the fetus (Quistad et al. 1982).

The results of Anadón and coworkers (Anadón et al. 1991b, 1996) indicate that the Type II pyrethroid, fluvalinate, may be more rapidly distributed than permethrin, a Type I pyrethroid, following dermal exposure in rats. These apparent differences in distribution of permethrin and fluvalinate could be the result of chemical or toxicokinetic differences in these pyrethroids or Type I and Type II pyrethroids in general, although no data are presently available to confirm or refute this possibility.

No information was located regarding distribution within tissues of pyrethroid compounds following oral exposure of humans or animals. No information was located regarding sex- or age-related differences in distribution of Type I and Type II pyrethroids following oral exposure of humans or animals.

3.4.2.3 Dermal Exposure

No information is available regarding distribution of Type I or Type II pyrethroids in humans following dermal exposure, and available data from animal studies are limited. In guinea pigs exposed to dermally applied permethrin, the concentration of permethrin measured in brain tissue 24 hours after dosing was 7-fold higher than that of plasma (Franz et al. 1996). Residual tissue concentrations of fenvalerate, but not of its metabolites, were determined 4 days after administration of a single dermal dose to goats (Mandal et al. 1996). The highest concentration was observed in the adrenal gland, followed by (in decreasing order) biceps muscle, omental fat, liver, kidney, lung, and cerebrum. Interpretation of these data is hindered because at the time of fenvalerate tissue content measurement, the majority of the dose had been eliminated (only small amounts of fenvalerate remained in plasma at 3 days after dosing). No additional studies were located concerning distribution of Type I or Type II pyrethroids to organs and tissues, and no information was available regarding age- or sex-related differences in distribution.

3.4.2.4 Other Routes of Exposure

No information was located regarding distribution of pyrethroids in humans following exposure by other routes.

Following intravenous administration in rats, Type I and Type II pyrethroids are rapidly and widely distributed to tissues and are concentrated in nervous tissue (Anadón et al. 1991b, 1996; Gray and Rickard 1982; Gray et al. 1980a; Silver and Dauterman 1989a). Plasma levels of parent compound exhibit a bi-phasic decline and fit a two-compartment model with rapid distribution phase (Anadón et al. 1991b, 1996). Distribution to the central nervous system is very rapid, with concentrations reaching peak levels within 5 minutes of administration (Gray et al. 1980a). Following intraperitoneal injection of rats with Type I pyrethroids, pyrethroids are rapidly distributed to the liver and are found to be associated with several subcellular fractions, including microsomes, indicating that pyrethroids are rapidly distributed to a detoxifying organ (Graillot and Hoellinger 1982). Results of these studies provide supportive evidence for the expectedly rapid and wide distribution of pyrethroids after absorption in humans.

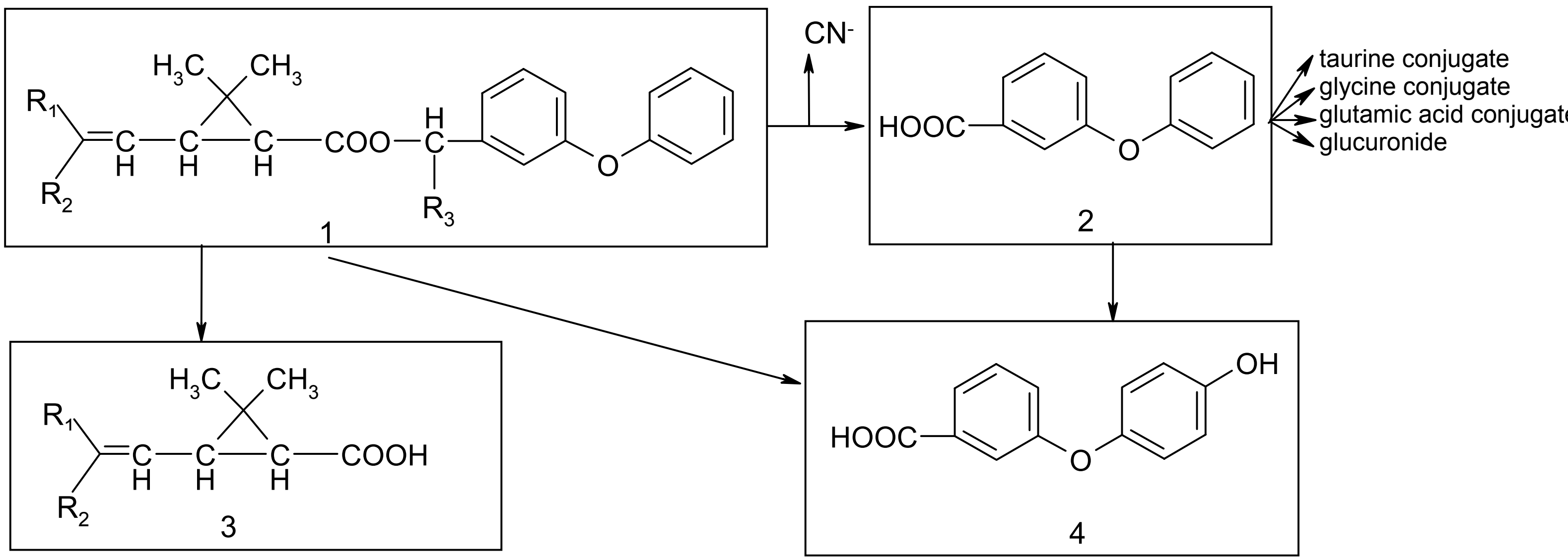
No information was located regarding sex- or age-related differences in distribution of pyrethroids following parenteral exposure.

3.4.3 Metabolism

Extensive study of the metabolic pathways involved in the biotransformation of pyrethroids in humans has not been undertaken. Information on the metabolism of Type I and Type II pyrethroid compounds in humans is based upon identification of pyrethroid metabolites in urine and blood obtained in a small number of studies conducted under controlled conditions or following occupational exposures. In contrast, the metabolism of Type I and Type II pyrethroid compounds has been extensively studied in several mammalian animal models. Since the metabolites that have been identified in humans have also been identified in other mammalian species, it is unlikely that there are significant qualitative differences between humans and other mammals in the major metabolic pathways for pyrethroids, although some species differences do undoubtedly exist (Anadón et al. 1991b; Eadsforth and Baldwin 1983; Eadsforth et al. 1988; Elliott et al. 1976; Gaughan et al. 1977; Leng et al. 1997a, 1997b; Woollen et al. 1992). The following summary of pyrethroid metabolism is based on the results of extensive investigations of the metabolism of pyrethroids in mammalian models. It is presumed that these metabolic pathways pertain to human metabolism of pyrethroid compounds although there may be important quantitative differences between species.

All synthetic pyrethroid compounds appear to be degraded by similar metabolic processes in mammals. Upon administration of pyrethroids to mammals, biotransformation takes place through hydrolysis of the central ester bond, oxidative attacks at several sites, and conjugation reactions to produce a complex array of primary and secondary water-soluble metabolites that undergo urinary and biliary excretion (Casida et al. 1983; Gray and Soderlund 1985; Leng et al. 1999a). It is widely accepted that metabolism results in the formation of compounds that have little or no demonstrable toxicity, although the formation of reactive or toxic intermediates cannot be ruled out, and it appears that cleavage of the ester bond results in substantial detoxification (Gray and Soderlund 1985; Hutson 1979). For halogenated pyrethroids (such as cyfluthrin, cypermethrin, and permethrin), rapid hydrolytic cleavage of the ester bond is followed by oxidation to yield carboxylic acid derivatives and phenoxybenzoic acid derivatives (Leng et al. 1997a, 1997b). These metabolites are, in general, excreted as alcohols, phenols, carboxylic acids, and their glycine, sulfate, glucuronide or glucoside conjugates (Aprea et al. 1997; Casida et al. 1983). Metabolic pathways for permethrin, cypermethrin and deltamethrin are shown in Figure 3-2. However, depending upon the type of pyrethroid compound, either oxidation or hydrolysis may predominate (Miyamoto 1976). The presence of the alpha-cyano group of the Type II pyrethroid compounds has been shown to decrease the rate of hydrolytic cleavage of the ester bond (Casida et al. 1983). Many of the trans enantiomers of pyrethroid compounds are metabolized mainly through hydrolytic cleavage of the ester linkage, with subsequent oxidation and/or conjugation of the component alcohol and acid moieties, whereas certain cis enantiomers are more resistant to hydrolytic attack and are degraded via oxidation at various sites of the molecule (Miyamoto 1976; Shono et al. 1979). For pyrethroids containing an alpha-cyanophenoxybenzyl substituent (Type II pyrethroids), cleavage of the ester bond results in the release of cyanide, which is rapidly converted mainly to thiocyanate (Casida et

Figure 3-2. Metabolic Diagram for Deltamethrin, Permethrin, and Cypermethrin



1 { deltamethrin $R_1 = R_2 = Br$ $R_3 = CN$
permethrin $R_1 = R_2 = Cl$ $R_3 = H$
cypermethrin $R_1 = R_2 = Cl$ $R_3 = CN$

2 { 3-phenoxybenzoic acid (3-PBA)

3 { 3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane carboxylic acid (DCVA)
3-(2,2-dibromovinyl)-2,2-dimethy-cyclopropane carboxylic acid (DBVA)

4 { 3-(4-hydroxy)-phenoxybenzoic acid (4-OHPBA)

al. 1983; Gray and Soderlund 1985; Ohkawa et al. 1979). It does not appear that there is significant additional metabolic fragmentation of the acid and alcohol moieties, since metabolism studies with ^{14}C-labeled pyrethroid compounds yield little or no detectable $^{14}CO_2$ (Ohkawa et al. 1979; Ruzo et al. 1978).

Information on the specific enzymes involved in metabolism of pyrethroid compounds is limited. Metabolism appears to involve nonspecific microsomal carboxyesterases and microsomal mixed function oxidases, which are located in nearly all tissue types (Casida et al. 1983; Miyamoto 1976; Shono et al. 1979). Since microsomal enzymes play an important role in the metabolism of pyrethroids, it is expected that many tissue types are potentially capable of rapidly metabolizing these compounds, with a particularly important role for the liver. Pyrethroids are metabolized in blood *in vitro* (Gray and Rickard 1982). Metabolism of pyrethroids may also occur in brain (Anadón et al. 1996; Ghiasuddin and Soderlund 1984), which may contribute to the detoxification of some pyrethroids in mammals (Ghiasuddin and Soderlund 1984).

Information on the effects of induction or inhibition of microsomal enzymes by other chemicals or drugs on the rate of metabolism of pyrethroid compounds in humans or animals was not identified.

No information was located regarding sex- or age-related differences in metabolism of pyrethroids following exposure in humans or animals.

3.4.3.1 Inhalation Exposure

The results of a single study of cyfluthrin in humans demonstrate that, when administered by the inhalation route, pyrethroids are rapidly metabolized, with metabolites appearing in the urine by 30 minutes after exposure (Leng et al. 1997a).

No studies were located regarding metabolism of pyrethroids following inhalation exposure to animals.

3.4.3.2 Oral Exposure

Given the important role of hepatic microsomal enzymes in the biotransformation of xenobiotics, accurate estimates of absorption following oral administration of pyrethroid compounds must take into account first-pass metabolism. Studies in humans indicate that the absorption of orally administered pyrethroids is incomplete; however, these studies do not provide evidence for first pass metabolism (Eadsforth and Baldwin 1983; Eadsforth et al. 1988; Woollen et al. 1992). Results of a study in isolated perfused rat liver are supportive for an important role for first-pass metabolism of pyrethroid compounds (Silver and Dauterman 1989b). In this study, the hepatic extraction ratios for both cis and trans isomers of tetramethrin were approximately 0.9 and both the cis and trans isomers were rapidly metabolized by the liver. If the high *in vitro* extraction is indicative of *in vivo*, then first pass extraction from the hepatic portal circulation and metabolism would be likely. Incomplete absorption of pyrethroids following oral exposure may also result from metabolism within the gastrointestinal tract or binding to poorly absorbed components of the ingesta. Results of studies in rats indicate that pyrethroid metabolites are produced within the gastrointestinal tract (Tomigahara et al. 1994b). Metabolites from permethrin were recovered in the feces following oral administration to rats, suggesting the possibility of metabolism in the gastrointestinal tract, or fecal elimination of metabolites formed after absorption (Gaughan et al. 1977).

Although no information is available regarding sex-related differences in metabolism following oral administration of pyrethroids in humans, no differences in metabolism were observed in male and female rats orally exposed to pyrethroids (Quistad et al. 1983).

3.4.3.3 Dermal Exposure

Little information is available regarding metabolism of pyrethroid compounds following dermal exposure. Following dermal application of permethrin to patients for treatment of scabies, permethrin metabolites were recovered from urine (van der Rhee et al. 1989). Results of a single study in volunteers comparing urinary metabolite profiles following oral and dermal exposure to cis- and trans-cypermethrin isomers demonstrated a difference in the urinary metabolite profiles following exposure by each route (Woollen et al. 1992). Following oral exposure, urine contained a higher proportion of trans-metabolites compared to that obtained following dermal exposure. These results could indicate differences in absorption or metabolism between these two routes of exposure.

No information was located regarding sex- or age-related differences in metabolism following dermal administration of pyrethroids to humans or animals.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

The results of a single study examining urinary metabolites in humans following inhalation exposure to cyfluthrin indicate that elimination follows first-order kinetics, with 93% of the urinary elimination complete within 24 hours of exposure (Leng et al. 1997a). Elimination half-times for the cyfluthrin metabolites cis-/trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (DCCA), 4-fluoro-3-phenoxybenzoic acid (FPBA), and their isomers ranged from 5.3 to 6.9 hours. These elimination half-times remained constant over a range of exposure levels, providing supportive evidence that pyrethroids exhibit first-order elimination kinetics. The amounts of cyfluthrin metabolites excreted in urine correlated with increasing exposure levels, demonstrating that urinary levels of pyrethroid metabolites may be a useful indicator of exposure level.

Several studies of occupational exposure of humans to pyrethroids were located; however, the exposures may have been by the inhalation, oral, or dermal routes, or a combination of these routes. Following occupational exposure to Type I and Type II pyrethroid compounds, excretion of pyrethroid metabolites in the urine occurs and is nearly complete within 4 days of exposure (Aprea et al. 1997; Chester et al. 1987; Kühn et al. 1999). Based on elimination of cyfluthrin from plasma, the elimination half-time is estimated to be between 0.5 and 2 hours (Leng and Lewalter 1999). Based on elimination of metabolites into the urine, the elimination half-time for cyfluthrin is 5 hours and for cypermethrin is 8 hours (Kühn et al. 1999). No information was provided in these studies regarding the amount of pyrethroid eliminated by nonurinary routes.

No information was located regarding sex- or age-related differences, or other factors, that might affect the elimination and excretion of pyrethroids following inhalation exposure of humans or animals.

3.4.4.2 Oral Exposure

Limited information is available regarding the elimination and excretion of Type I and Type II pyrethroid compounds following oral exposure in humans. The elimination half-time of cis-permethrin in plasma following ingestion of a mix of cis and trans isomers of permethrin in a suicide attempt was approximately 67 hours (Gotoh et al. 1998). Trans-permethrin was eliminated from the blood more quickly than the cis isomer and was undetectable in blood after 25 hours. However, an estimate of the plasma elimination half-time for the trans isomer was not reported. This patient was noted to have a history of chronic renal dysfunction, but no specific details were reported. Therefore, it is not possible to determine how this patient’s renal status may have affected the elimination of permethrin from the plasma. In humans exposed to single oral doses of Type II pyrethroids, the elimination half-time based on the appearance of metabolites in the urine has been estimated to be between 6 and 13 hours (Leng et al. 1997b; Woollen et al. 1992). Approximately 35–50% of the administered dose was excreted in the urine as metabolites during the first 5 days after dosing, with peak urinary excretion rates observed during the first 24 hours after dosing (Eadsforth and Baldwin 1983; Eadsforth et al. 1988; Leng et al. 1997b; Woollen et al. 1992). It is not possible to determine the percentage of the administered dose that was eliminated in the urine in these studies since only the urinary pyrethroid metabolites, and not total urinary pyrethroids (parent compound plus metabolites), were measured. Fecal elimination following oral dosing of Type II pyrethroids in humans has been confirmed based on the results of one study in humans, but neither the fraction of the administered dose excreted in feces nor the identity of the compounds excreted in feces were determined (Stockis et al. 1985).

Results of animal studies indicate that Type I and Type II pyrethroids are almost completely eliminated from the body within 4–12 days following oral exposure, with the majority of the dose eliminated within the first 12–48 hours (Anadón et al. 1996; Elliott et al. 1976; Gaughan et al. 1977; Hunt and Gilbert 1977; Lee et al. 1985; Quistad and Selim 1983; Quistad et al. 1982; Ridlen et al. 1984; Ruzo et al. 1978; Staiger and Quistad 1984; Wszolek et al. 1980). Type I and Type II pyrethroids exhibit first-order elimination kinetics. An estimate for the elimination half-time of permethrin in rats is approximately 8 hours (Anadón et al. 1991b). In oral studies, the plasma elimination half-time for fluvalinate in Rhesus monkeys was 2–3 hours, whereas, in rats, the elimination half-time of deltamethrin was 38.5 hours, although the time from administration to peak levels of the pyrethroids in both studies was similar (approximately 2–3 hours) (Anadón et al. 1996; Quistad and Selim 1983). It is not known if the differences in the elimination half-times observed in these studies are related to species differences, differences in dose, or differences in the elimination kinetics of the specific pyrethroid compounds.

In monkeys, cows, and rats, a large portion of the orally administered dose (43–56%) is excreted in the urine (Quistad and Selim 1983; Quistad et al. 1982; Ridlen et al. 1984; Staiger and Quistad 1984), primarily as metabolites. In rats subject to oral exposure, almost all of the pyrethroids recovered in the urine are metabolites, with urine containing very little of the unchanged compound (Ueda et al. 1975b). In monkeys, cows, and rats, approximately 45–60% of the orally administered dose is excreted in the feces as a mix of parent compound and metabolites (Miyamoto et al. 1968; Quistad and Selim 1983; Quistad et al. 1982; Ridlen et al. 1984; Staiger and Quistad 1984; Ueda et al. 1975b). The urinary excretion route appears to be more important for trans-permethrin metabolites, while the fecal excretion route appears to be more important for cis-permethrin metabolites (Elliott et al. 1976; Hunt and Gilbert 1977).

Studies performed using cows, rats, and monkeys indicate that pyrethroids undergo biliary excretion, although estimates for the amount of biliary excretion were not available in these studies (Quistad and Selim 1983; Quistad et al. 1982, 1983). Based on the results of a study in isolated perfused rat liver, it appears that tetramethrin may undergo extensive biliary excretion (Silver and Dauterman 1989b). Studies in lactating cows and goats indicate that only very low levels of Type I pyrethroids are excreted (<1% of the administered dose) in milk (Gaughan et al. 1978; Hunt and Gilbert 1977; Quistad et al. 1982; Ridlen et al. 1984; Wszolek et al. 1980). In one study, one pregnant cow was administered a single oral dose of ^{14}C-fluvalinate and tissues were examined for radioactivity 8 days after dosing (Quistad et al. 1982). Analysis of the ^{14}C content of the fetus indicates minimal transfer of fluvalinate or its metabolites to the fetus (approximately 1×10^{-5}% of the administered dose). It does not appear that pyrethroids are excreted in significant amounts via expired air (Gaughan et al. 1977; Ohkawa et al. 1979; Ruzo et al. 1978; Ueda et al. 1975b).

Apart from the finding that pyrethroids may be excreted in milk, no additional information was located regarding sex-related differences, and no information was located regarding age-related differences, that might affect the elimination and excretion of pyrethroids following oral exposure of humans or animals.

3.4.4.3 Dermal Exposure

Limited information is available regarding elimination and excretion of pyrethroids following dermal exposure in humans. Results of two studies in humans exposed to single dermal doses of cypermethrin indicate that a small fraction (0.1–1.2%) of the administered dose is excreted in the urine as metabolites (Eadsforth et al. 1988; Woollen et al. 1992). Peak urinary excretion rates were observed between 12 and 36 hours after dosing (Woollen et al. 1992). Following dermal application of a single permethrin dose to patients for treatment of scabies, permethrin metabolites were excreted in urine, with urinary excretion persisting for 7 days after exposure (van der Rhee et al. 1989).

In rats exposed to single dermal doses of permethrin, >90% of the absorbed dose was excreted in urine and feces, with a urine-to-fecal ratio of approximately 4:1 (Shah et al. 1987). While results of this study may provide evidence for fecal excretion following exposure by a nonoral route, it is possible that oral exposure occurred through licking of the application site if the animals were not properly restrained. In this study, no differences were noted in urinary excretion between young and adult rats. No other studies were located in which age-related differences in elimination and excretion of pyrethroids or their metabolites were assessed following dermal exposure. Following dermal exposure of rats to ^{14}C-fluvalinate, 0.7 and 0.8% of the administered radioactivity was excreted in the urine and feces, respectively (Quistad et al. 1983). In this study, one group of animals was not restrained and the animals were able to lick the application site, which may have resulted in oral exposure and higher urinary and fecal excretion of ^{14}C.

No information was located regarding sex-related differences, or other factors, that might affect the elimination and excretion of pyrethroids following dermal exposure in humans or animals.

3.4.4.4 Other Routes of Exposure

No information was located regarding the elimination and excretion of Type I or Type II pyrethroids in humans following parenteral exposure. In rats administered a mix of cis- and trans-tetramethrin intravenously, the elimination half-time for the cis isomer was less (72 minutes) than that observed for the trans isomer (125 minutes) (Silver and Dauterman 1989a). Following intravenous administration to the rats, tetramethrin metabolites were recovered from both urine and, to a lesser extent, feces, providing evidence for biliary excretion. No unmetabolized tetramethrin was recovered in the urine. Only a small amount of the parent cis isomer was identified in the feces. Fecal excretion appears to be the major excretory pathway for the cis isomer, whereas urinary excretion appears to be the major excretory route for the trans isomer. Thus, biliary elimination appears to be more important for the cis isomer than for the trans isomer. In rats administered deltamethrin and its metabolite (4-OH-deltamethrin) intravenously, elimination half-times were 33 and 25 hours, respectively. In another phase of this study involving gavage administration, similar elimination rates were observed (Anadón et al. 1996).

No information was located regarding age- or sex-related differences that might affect the excretion and elimination of pyrethroids following parenteral exposure in humans or animals.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

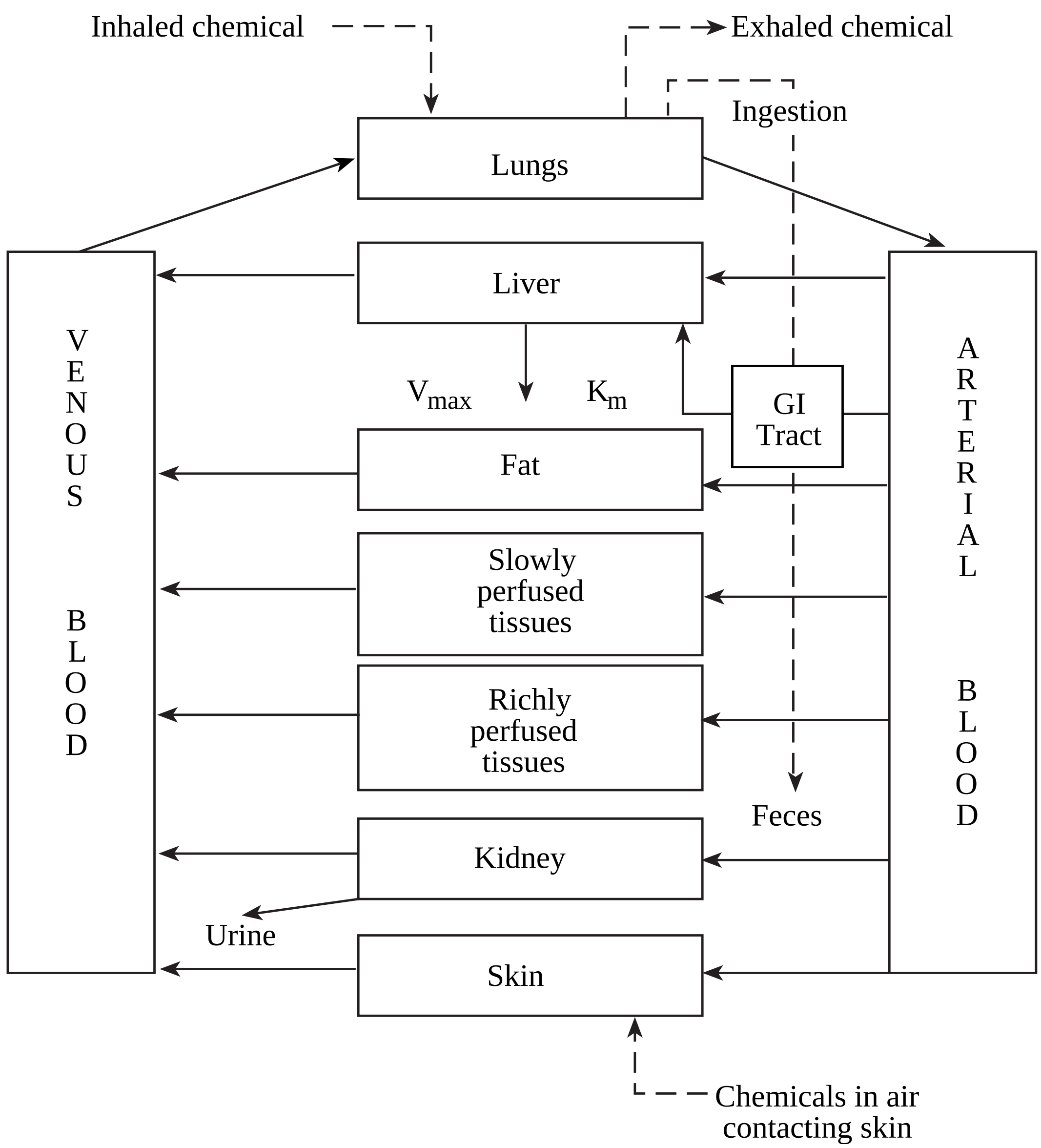
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

No PBPK models for exposure to pyrethroid compounds were identified. Thorough study of the toxicokinetic profiles of Type I and Type II pyrethroids in humans or experimental animals has not been undertaken. Empirical models for exposure to Type I (permethrin) and Type II (deltamethrin) pyrethroids have been developed based upon the results of two studies in rats (Anadón et al. 1991b, 1996). The empirical models developed from these toxicokinetic studies yielded similar results for both compounds, indicating that the biodisposition of Type I and Type II compounds is similar. Pyrethroids are rapidly absorbed following oral exposure. Following oral and intravenous exposure, permethrin and deltamethrin plasma kinetics are described by a two-compartment model with a relatively rapid distribution phase, followed by a slower elimination phase. Following intravenous administration, the distribution and elimination half-times for permethrin were 0.46 and 8.67 hours, respectively, and for

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

deltamethrin were 1.39 and 33.0 hours, respectively. Under these experimental conditions, permethrin was eliminated more rapidly than deltamethrin.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. No information was located regarding the mechanism of absorption of pyrethroids from the gastrointestinal tract. Since pyrethroids are lipophilic compounds, it is presumed that they cross intestinal cells and pass into the circulation by diffusion across lipid membranes. No information was identified on the location of absorption of pyrethroids within the gastrointestinal tract. However, it is presumed that most of the absorption takes place in the intestines due to the large exposed surface area. Although no information was located regarding the mechanism of absorption through the skin or across alveolar membranes, it is presumed that pyrethroids cross these barriers by diffusion across lipid membranes.

Distribution. No information was located regarding the transport of pyrethroid compounds in blood. Pyrethroids are distributed to nearly all tissues and are concentrated in tissues with high lipid contents, such as fat and nerve tissue (Anadón et al. 1991b, 1996). It is likely that the pattern of concentration in lipid-rich tissues is due to the high lipid solubility of pyrethroid compounds. Since metabolism of pyrethroids results in products that are more water-soluble than the parent compounds, it is likely that the metabolites are less able to cross the blood-brain barrier, unless there are facilitated mechanisms for transport of pyrethroid metabolites that have not yet been characterized.

Metabolism. Upon administration of pyrethroids to mammals, biotransformation takes place through hydrolysis of the central ester bond, oxidative attacks at several sites, and conjugation reactions to produce a complex array of primary and secondary water-soluble metabolites that undergo urinary excretion (Casida et al. 1983; Gray and Soderlund 1985; Leng et al. 1999a, 1999b). It is well accepted that these metabolites have little or no demonstrable toxicity, although the formation of reactive or toxic intermediates cannot be ruled out, and it appears that cleavage of the ester bond results in detoxification (Gray and Soderlund 1985). For halogenated pyrethroids (such as cyfluthrin, cypermethrin, and permethrin), rapid hydrolytic cleavage of the ester bond is followed by oxidation to yield carboxylic acid derivatives and phenoxybenzoic acid derivatives (Leng et al. 1997a, 1997b). These metabolites are then generally metabolized further and form conjugated products with compounds such as glycine, sulfate, and glucuronic acid (Aprea et al. 1997; Casida et al. 1983). Information on the specific enzymes involved in metabolism of pyrethroid compounds is limited. Metabolism appears to involve nonspecific microsomal carboxyesterases and microsomal mixed function oxidases, which are located in nearly all tissue types.

Excretion. No information was located regarding the specific mechanisms of excretion of pyrethroid compounds. However, metabolism of pyrethroids results in products that are water soluble and, therefore, more readily eliminated from the body by renal and biliary excretion. No information is available regarding the mechanisms of excretion of pyrethroids and pyrethroid metabolites by the kidney, but it is expected that pyrethroids and their metabolites are eliminated, at least in part, by glomerular filtration since their molecular size is not restrictive for passage though the glomerular membrane. However, there is no information on the extent to which these compounds bind to plasma proteins, which might restrict their glomerular filtration. No information was located regarding mechanisms of excretion for the biliary or salivary routes of elimination. No information was located regarding mechanisms involved in the passage of pyrethroids into milk, although excretion into milk most likely occurs via lipid diffusion across membranes with retention in milk fat.

3.5.2 Mechanisms of Toxicity

The primary site of action for pyrethrins and pyrethroids is the sodium channel of nerve cells, as is also the case for DDT and its analogs (for reviews, see Cassida et al. 1983; Coats 1990; Narahashi 1985; Sattelle and Yamamoto 1988; Soderlund 1995; Valentine 1990; Vijverberg and van den Bercken 1990). Using a variety of methods, including voltage clamp and patch clamp techniques, it has been shown that pyrethrins and pyrethroids slow the closing of sodium channel gates following an initial influx of sodium during the depolarizing phase of an action potential, which results in a prolonged sodium tail current (Narahashi 1986; Vijverberg and Van den Bercken 1982). Two different types of pyrethroids are recognized, based on differences in basic structure (the presence or absence of a cyano group in the alpha position), and the symptoms of poisoning (Coats 1990; Verschoyle and Aldridge 1980). Type I pyrethroids do not include a cyano group; their effects in rodents typically include rapid onset of aggressive behavior and increased sensitivity to external stimuli, followed by fine tremor, prostration with coarse whole body tremor, elevated body temperature, coma, and death. The term T-syndrome (from tremor) has been applied to Type I responses. Type II pyrethroids include a cyano group; their effects in rodents are usually characterized by pawing and burrowing behavior, followed by profuse salivation, increased startle response, abnormal hind limb movements, and coarse whole body tremor that progresses to sinuous writhing (choreoathetosis). Clonic seizures may be observed prior to death. Body temperature is not increased, but may decrease. The term CS-syndrome (from choreoathetosis and salivation) has been applied to Type II responses. Two of the cyano-pyrethroids, fenpropathrin and cyphenothrin, have been shown to trigger responses intermediate to those of T-syndrome and CS-syndrome, characterized by both tremors and salivation (Miyamoto et al. 1995; Wright et al. 1988). Mechanisms underlying this intermediate response type have not been elucidated. Occupational exposure to pyrethroids (particularly Type II pyrethroids containing the cyano group) frequently leads to paresthesia (abnormal cutaneous sensations such as tingling, burning, numbness, and itching). This response is considered to result from the direct action of pyrethroids on sensory nerve endings (LeQuesne and Maxwell 1980; Wilks 2000), causing repetitive firing in these fibers (Vijverberg and van den Bercken 1990).

Marked differences exist in the duration of action on the sodium channel gate, particularly between Type I and Type II pyrethroids. These differences may account for the differences observed in toxic effects elicited in laboratory animals. Measurements of sodium tail currents in frog nerve fibers treated with Type I pyrethroids measure approximately 6–150 milliseconds in duration, whereas those generated from Type II pyrethroids last much longer (290 milliseconds to as long as several seconds) (Narahashi 1986; Vijverberg et al. 1986). The shorter-duration sodium tail current generated by Type I pyrethroids results in an elevated after potential that may cause repetitive discharges. The longer-duration sodium tail current generated by Type II pyrethroids may result in summation of after potentials, which can cause gradual depolarization of the nerve and frequency-dependent suppression of action potentials. For both Type I and Type II pyrethroids, the magnitude of effect on sodium influx is strongly dependent on temperature, increasing markedly with cooling (Narahashi 1971, 1976; Vijverberg et al. 1983). The action of pyrethroids on as little as 0.6% of the sodium channel gates results in repetitive after-discharges that could lead to neurotoxic symptoms in animals (Narahashi 1996; Song and Narahashi 1996).

Pyrethroids appear to bind to the membrane lipid phase in the immediate vicinity of the sodium channel, thus modifying the channel kinetics. Results of radioligand binding assays indicate that the actions of DDT and pyrethroids on the sodium channel are site-specific, functionally distinct from, but allosterically coupled to, Sites 2, 3, and 5 of the 5 known neurotoxin-binding domains of the sodium channel (Lombet et al. 1988). Pyrethroids do not appear to influence sodium channel properties such as cation selectivity and cation binding (Yamamoto et al. 1986).

Stereochemistry dictates the degree of toxicity that will be expressed by a given pyrethroid formulation or mixture. In the case of tetramethrin, like all other Type I pyrethroids, the 1R conformation is considerably more toxic than the 1S conformation. The 1S isomer can also inhibit toxicity by competitive inhibition at a number of stereospecific pyrethroid binding sites, thus preventing binding of the more toxic 1R isomer (Narahashi 1986). Furthermore, it has been observed that the cis isomers possess greater mammalian toxicity than the trans isomers. For these reasons, recent formulations of tetramethrin (d-tetramethrin) contain predominantly the 1R cis and 1R trans isomers in a ratio of 20:80 (Tomlin 1997).

Type II pyrethroids have been shown to inhibit specific binding at or near the picrotoxin site of $GABA_A$ receptors in mouse brain (Crofton et al. 1987; Lawrence and Casida 1983), specifically inhibiting GABA-dependent chloride flux (Bloomquist et al. 1986). However, taken together, the results of a number of studies that investigated the actions of pyrethrins and pyrethroids on ligand-gated ion channels indicate a limited role for the $GABA_A$ receptor in pyrethroid-induced neurotoxicity (Bloomquist 1993).

Recently, Forshaw et al. (2000) demonstrated that voltage-gated chloride channels may play a role in Type II, but not Type I, pyrethroid poisoning. Their patch test experiments showed that ivermectin and pentobarbitone significantly increased open chloride channel probability in mouse neuroblastoma cells. When rats were pretreated with ivermectin or pentobarbitone and subsequently administered the Type II pyrethroid deltamethrin, comparatively reduced severity of neurotoxic effects was observed. This was an indication that these chemicals effectively antagonized Type II pyrethroid poisoning. Changes in neurotoxic effects were not observed when the Type I pyrethroid, cismethrin, was used.

Other pyrethroid-induced effects include altered concentrations of catecholamines, blood glucose, and lactate, and marked changes in cerebral blood flow. However, these effects may be secondary effects arising from neural dysfunction resulting from the action of pyrethroids on the sodium and chloride channels.

3.5.3 Animal-to-Human Extrapolations

Limited information is available regarding the specific mechanisms involved in the toxicokinetics of pyrethroids in either humans or animals. Therefore, it is difficult to assess how the toxicokinetic data obtained from studies in laboratory animals may differ from that obtained in humans. It is presumed that the toxicokinetic mechanisms involved are generally similar in all mammalian species, although quantitative interspecies differences most certainly exist. Absorption and distribution of pyrethroids appear to be largely determined by the lipid-soluble nature of these compounds. Therefore, it is expected that the absorption and distribution of pyrethroids in humans will be similar to that observed in other mammalian species. In both humans and animals, pyrethroids appear to be metabolized by nonspecific microsomal carboxyesterases and microsomal mixed function oxidases, which are located in nearly all tissue types and are common to all mammalian species. Since the metabolites that have been identified in humans have also been identified in other mammalian species, it is unlikely that there are significant qualitative differences between humans and most animal species for the major metabolic pathways for pyrethroids (Anadón et al. 1991b; Eadsforth and Baldwin 1983; Eadsforth et al. 1988; Elliott et al. 1976; Gaughan et al. 1977; Leng et al. 1997b; Woollen et al. 1992). The cat appears to be an exception, exhibiting increased sensitivity to the toxic actions of pyrethroids. This increased sensitivity may be the result of less efficient hepatic glucuronidation in the cat (Whittem 1995), a second step in the metabolism of pyrethroids in mammalian systems. Pyrethroids and their metabolites are excreted primarily in the urine and feces, and it is likely that mechanisms involved are the same in all mammalian species. If interspecies differences exist in sodium channel kinetics, such differences could increase the uncertainty related to interspecies extrapolation.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Thomas (1992) and again by Colborn (1993), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine

Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors.* In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

The potential for pyrethroids to act as endocrine disruptors has been investigated in a limited number of studies *in vitro* (Eil and Nisula 1990; Garey and Wolff 1998; Go et al. 1999). Using Ishikawa Var-I human endometrial cancer cell line and the T47D human breast cancer cell line, cell lines that produce phosphatase as an indicator of hormonal activity, Garey and Wolff (1998) demonstrated that fenvalerate and phenothrin induced significant estrogenicity at concentrations of 10 μM. Similar tests performed using d-trans-allethrin and permethrin did not result in apparent estrogenicity. None of the 4 pyrethroids showed significant estrogen antagonist activity or acted as progestins, but fenvalerate and d-trans-allethrin significantly antagonized the action of progesterone in T47D cells. Go et al. (1999) found that micromolar concentrations of phenothrin or fenvalerate induced pS2 expression in the MCF-7 human breast cell carcinoma cell line by 5-fold, indicating that these pyrethroids may induce estrogenic activity. The fact that phenothrin-induced pS2 expression was suppressed by antiestrogen co-treatment is a further indication that phenothrin may affect endocrine function. Several pyrethroids have been shown to interact with androgen binding sites in dispersed intact human genital skin fibroblasts, with varying degrees of potency, but at levels comparable to those resulting in the same order of binding observed using cimetidine, a known inhibitor of androgen receptor binding (Eil and Nisula 1990). Pyrethrins and bioallethrin were found to displace [^{3}H]testosterone from sex hormone binding globulin in human plasma, at inhibitory levels up to 50% (Eil and Nisula 1990).

Data regarding potential for pyrethrins and pyrethroids to act as endocrine disruptors *in vivo* include findings of reduced reproductive organ weights, significantly altered sperm characteristics, and reduced plasma testosterone levels in male rats administered oral doses of pyrethroids for up to 65 days (Abd El-Aziz et al. 1994; Abd El-Khalek et al. 1999; Hassan et al. 1993).

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Differences between children and adults regarding the toxicokinetics of pyrethroid compounds have not been investigated in humans, and there is insufficient information from studies conducted in immature laboratory animals to allow for prediction of particular sensitivities in children. However, based on what is known about the toxicokinetics of pyrethroid compounds, some general areas of concern for exposure of children to pyrethroids can be identified.

Limited information is available regarding the ability of pyrethroid compounds to cross the placenta and be distributed to the fetus. Measurements of radioactivity in fetuses of rats administered radiolabeled pyrethroids indicated that <0.004% of the administered dose of the Type I pyrethroid, tetramethrin, was recovered in the fetus (Kaneko et al. 1984b). Recovered activity from radiolabeled fenvalerate (a Type II pyrethroid) was <0.07% (Shiba et al. 1990). Eight days after a pregnant cow was given a single a single dose of ^{14}C-fluvalinate, only trace amounts (approximately 1x10^{-5}% of the administered dose) of ^{14}C were detected in the fetus (Quistad et al. 1982). However, given the fact that exposure of rat fetuses to pyrethroids via their mothers resulted in persistent alterations in brain neurotransmitter numbers (Malaviya et al. 1993), it would appear that concentrations that reached the fetal brain were sufficient to cause a consistent effect.

Pyrethroids are eliminated from the body primarily by metabolism and subsequent excretion of metabolites via the urine and feces. Hepatic metabolism of pyrethroids is of critical importance for the detoxification and, ultimately, the excretion of these compounds. Although biotransformation reactions are catalyzed largely by microsomal enzymes, and enzymatic activity is involved in conjugation reactions, the specific enzymes involved in pyrethroid metabolism have not been identified. The ability of children to detoxify pyrethroid compounds through metabolic pathways may be different from that of adults (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Using lethality as an indicator of toxicity in a study designed to assess age-related susceptibility to pyrethroids, Cantalamessa (1993) administered acute oral doses of permethrin or cypermethrin to 8-, 16-, and 21-day-old rats, as well as adult rats. For both permethrin and cypermethrin, acute oral LD_{50} values increased with increasing age, indicating greater sensitivity in younger rats. No significant changes in LD_{50} values were seen in young rats pretreated with either tri-o-tolyl phosphate (TOTP, an esterase inhibitor) or piperonyl butoxide (PB, a monooxygenase inhibitor). However, TOTP pretreatment in adult rats resulted in a significant increase in pyrethroid-induced lethality. Increased lethality in adult rats pretreated with PB did not reach the level of statistical significance. These results suggest the possibility that increased susceptibility of young animals to pyrethroid poisoning may be related to less efficient enzyme production than in adult animals. If children have a decreased metabolic capacity compared to adults, altered distribution and excretion of pyrethroids could result. Since pyrethroid metabolites are water-soluble compounds, it is likely that their ability to cross the blood-brain barrier is limited. In children, a decrease in the production of these polar metabolites could result in an increased distribution of unmetabolized pyrethroids to the central nervous system. There also could be an increase in the distribution of pyrethroids to the central nervous system due to immature development of the blood-brain barrier. Very little unmetabolized pyrethroid is excreted in the urine, most likely because pyrethroid compounds are very lipid soluble and, if filtered by the glomerulus, are likely to undergo extensive renal reabsorption via lipid diffusion. If the metabolism of pyrethroids is decreased in children, a decrease in the renal excretion of pyrethroids may occur. Since specific details on the mechanisms of the renal handling of pyrethroids are not known, it is unclear how immature renal functions may affect the excretion of pyrethroids and pyrethroid metabolites in newborns and young children.

Exposure to pyrethroids through ingestion of breast milk in nursing infants has not been investigated in humans. However, only very low levels of pyrethroids (<1% of the orally administered dose) are excreted into milk of lactating cows and goats, which would suggest that exposures in human by this route may be similarly low (Gaughan et al. 1978; Hunt and Gilbert 1977; Quistad et al.1982; Ridlen et al. 1984; Wszolek et al. 1980). The relatively low transfers of lipophilic pyrethroids to milk presumably reflects competing pathways of elimination, including relatively rapid and extensive metabolism to more water-soluble metabolites and excretion in urine and feces.

Pyrethroids do not appear to impair morphological development in animals at the gross or histological level. However, exposure of young neonatal animals may result in neurological changes that become apparent when tested as adults (Ahlbom et al. 1994; Eriksson and Fredriksson 1991; Talts et al. 1998a). Mice, given oral doses of bioallethrin or deltamethrin on postpartum days 10–16 (a period of rapid brain development) at levels well below those expected to result in overt signs of neurotoxicity, first showed significantly increased spontaneous motor activity when tested as adults. Although these studies do not conclusively indicate that young animals are more susceptible to pyrethroid poisoning than adults, they do suggest that less obvious and long-lasting effects can be elicited at early, and possibly more vulnerable, stages of growth.

Children may be more likely to be exposed to pyrethroids than adults. Behavioral patterns of children can result in higher rates of ingestion of soil and dust, which may contain pyrethroid compounds following spraying. Examples of activities that tend to promote soil and dust ingestion preferentially in children include playing and crawling on the ground and floor, hand-to-mouth activity, mouthing of objects, and indiscriminate eating of food items on the ground or floor. Pyrethroids are also used in shampoos and creams for treatment of patients with lice and scabies. Hand-to-mouth behavior may increase the risk of exposure in children under these conditions of use.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to pyrethrins and pyrethroids are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by pyrethrins and pyrethroids are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations that are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Pyrethrins and Pyrethroids

Measurement of urinary metabolites of pyrethroids may serve as biomarkers of exposure. In several studies in humans exposed to pyrethroids occupationally, the presence of pyrethroid metabolites in urine has been used to confirm exposure (Aprea et al. 1997; Kühn et al. 1999; Leng et al. 1996, 1997a, 1997b). Chemically, synthetic pyrethroids are esters of chrysanthemic acid and specific alcohols, such as 3-phenoxybenzyl alcohol. Hydrolytic cleavage of the ester bond *in vivo* yields chrysanthemic acid derivatives and 3-phenoxybenzoic (3-PBA) (Aprea et al. 1997; Kühn et al. 1999; Leng et al. 1997a, 1997b). The specific pyrethroid metabolites found in urine varies depending upon the parent compound, which may have some modifications to the chrysanthemic acid moiety (Kühn et al. 1999). Results of a single study in humans following inhalation exposure to cyfluthrin indicate that the amounts of cyfluthrin metabolites excreted in urine correlate with increasing exposure levels (Leng et al. 1997a). Thus, urinary levels of pyrethroid metabolites may be a useful indicator of exposure level; however, at this time, there is insufficient information to allow for correlation of the amount of metabolites measured in the urine to the body burden of pyrethroids or to the level of exposure to pyrethroids.

3.8.2 Biomarkers Used to Characterize Effects Caused by Pyrethrins and Pyrethroids

Paresthesia (an abnormal cutaneous sensation sometimes described as tingling, burning, stinging, numbness, and itching) has been widely reported among individuals occupationally exposed to pyrethroids (see Vijverberg and van den Bercken 1990 for a summary of available information on occupationally-induced paresthesia). Other symptoms associated with occupational exposure to pyrethroids include dizziness, headache, nausea, loss of appetite, blurred vision, and tightness of the chest. Mild acute pyrethroid poisoning is characterized in part by listlessness and muscular fasciculations. Increased peripheral nerve excitability was measured in cotton workers following 3 days of exposure to deltamethrin during spraying. Whereas paresthesia may be a biomarker of effect for humans occupationally exposed to pyrethroids, other reported symptoms are not specifically indicative of pyrethrin or pyrethroid poisoning.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Pyrethroids are eliminated through biotransformation reactions that are catalyzed by microsomal enzymes, although the specific enzymes involved have not been identified. Results from studies of laboratory animals show that inhibition of hydrolytic reactions and of oxidative metabolism increases the toxicity of pyrethroids, while induction of microsomal oxidases decreases the toxicity of pyrethroids (Hutson 1979). Therefore, it appears that chemicals or drugs capable of inducing or inhibiting the enzymes involved in pyrethroid biotransformation reactions can alter the metabolism of pyrethroids. Since the metabolites of pyrethroids are more water soluble than the parent compounds, they are less likely to cross the blood-brain barrier and are more easily excreted by the kidney and liver than the parent compounds. Thus, alterations in the metabolism of pyrethroids through inhibition or induction of microsomal enzymes could alter the distribution and excretion of pyrethroids. For example, piperonyl butoxide, a common insecticide synergist, inhibits microsomal enzymes and potentiates the toxic effects of pyrethrins and pyrethroids to mammals.

Limited evidence exists to suggest that some Gulf War veterans with chronic, nonspecific symptoms may be experiencing neurological dysfunction due to low-level exposures to mixtures of anti-cholinesterase agents, insect repellents, and pyrethroids that might have additive or synergistic effects (Haley and Kurt 1997; Haley et al. 1997a, 1997b). To test this hypothesis, McCain et al. (1997) administered rats oral doses of a short-acting anti-cholinesterase agent (pyridostigmine bromide), an insect repellent (DEET), and permethrin, alone or in combination, and found that combined exposure resulted in a higher degree of lethality than that which would be expected from additive lethal values obtained for each chemical separately. These findings were suggestive of a synergistic (greater than additive) effect. However, in a study of percutaneous absorption of DEET and permethrin across mouse skin *in situ*, both separately and in combination, it was found that DEET appeared to inhibit the absorption of permethrin (Baynes et al. 1997). Synergistic effects with other chemicals could potentially occur in workers who spray a variety of pesticides, although no data were available to indicate such effects.

Another indication of an adverse toxic interaction between pyrethroids and other chemicals is the finding of significantly increased chromosomal aberrations in bone marrow cells of rats orally administered repeated doses of cypermethrin and lead, in combination (Nehéz et al. 2000). This effect was significant when compared with both control animals and those administered cypermethrin or lead separately, and appeared to be greater than an additive effect.

See Section 3.11.3 for information regarding chemicals used to reduce the toxic effects of pyrethrins and pyrethroids.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to pyrethrins or pyrethroids than will most persons exposed to the same level of pyrethrins or pyrethroids in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of pyrethrins or pyrethroids or compromised function of organs affected by pyrethrins or pyrethroids. Populations who are at greater risk due to their unusually high exposure to pyrethrins or pyrethroids are discussed in Section 6.7, Populations with Potentially High Exposures.

Pyrethroids are eliminated from the body primarily by metabolism and subsequent excretion of metabolites into the urine. Individuals with impaired liver function that results in decreased ability to metabolize pyrethrins or pyrethroids are likely to have increased susceptibility to the toxic effects of pyrethrins or pyrethroids. Since urine and bile are the major excretory routes for pyrethrin and pyrethroid metabolites, kidney and/or liver disease are likely to delay elimination of metabolites from the body. However, no studies were located in which metabolites of pyrethrins or pyrethroids were shown to exert toxic effects in humans or animals. Young animals may be more susceptible during stages when enzymes responsible for metabolizing absorbed pyrethroids are not fully developed (Cantalamessa 1993). Young animals may also be more susceptible to neurological damage if exposed to pyrethroids during critical stages of neonatal brain development (Ahlbom et al. 1994; Eriksson and Fredriksson 1991; Talts et al. 1998a).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to pyrethrins or pyrethroids. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to pyrethrins. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to pyrethrins:

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. 2nd edition. Baltimore: Williams & Wilkins. 1626-1627.

Goldfrank LR, Flomenbaum NE, Lewin NA, et al., eds. 1998. Goldfrank's toxicologic emergencies. 6th edition. Stamford: Appleton & Lange. 1455-1456.

Haddad LM, Shannon MW, Winchester JF, eds. 1998. Clinical management of poisoning and drug overdose. 3rd edition. Philadelphia: W.B. Saunders. 482-483.

3.11.1 Reducing Peak Absorption Following Exposure

Inhalation Exposure. There is little information regarding the degree of absorption following inhalation exposure to pyrethrins or pyrethroids, although it is presumed that absorption will occur via diffusion across lipid membranes. However, there is no known effective way to reduce absorption following inhalation exposure to pyrethrins or pyrethroids.

Oral Exposure. Pyrethrins and pyrethroids are rapidly absorbed following oral exposure and it is presumed that absorption occurs across the intestinal mucosa via diffusion. There is, however, very little information available regarding the rate or extent of absorption following oral administration in humans. Use of lavage and activated charcoal would likely result in reduced absorption following oral exposure, and charcoal may aid in removing compounds undergoing enterohepatic recirculation. It is also presumed that some absorption could occur in the mouth and stomach and, therefore, mouth rinsing may modestly contribute to decreasing absorption following oral exposure.

Dermal Exposure. Pyrethrins and pyrethroids are not well absorbed following dermal exposure, but limited absorption through the skin does occur. Washing of the skin with soap and water would reduce dermal absorption. If the eyes are affected, proper rinsing procedures should be followed.

No information was located regarding the effectiveness of various methods intended to reduce peak absorption of pyrethrins or pyrethroids following exposure.

3.11.2 Reducing Body Burden

No information was located regarding the effectiveness of various methods intended to reduce pyrethrin or pyrethroid body burden following absorption.

Pyrethrins and pyrethroids are substantially detoxified through biotransformation reactions catalyzed by microsomal enzymes, although the specific enzymes involved have not been identified. It is anticipated that the body burden would be reduced more quickly if these enzymes are induced; however, until the specific enzymes involved are identified, it is not possible to specify protocols to reduce the body burden of pyrethrins or pyrethroids through induction of microsomal enzymes. Metabolites of pyrethrins and pyrethroids are excreted in urine and bile, but no specific information is available regarding the renal or hepatic handling of these metabolites. Increased fluid consumption, which increases the rate of urine production and excretion, may help to decrease the body burden of pyrethroid metabolites since they are water soluble and excreted in the urine. Activated charcoal might aid in removing pyrethrins or pyrethroids undergoing enterohepatic circulation. However, since pyrethrins and pyrethroids are rapidly metabolized by mammalian detoxification systems, such methods for reducing body burden might not effectively shorten the time during which pyrethrins and pyrethroids exert their toxic effects.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No information was located regarding effective methods for interfering with the mechanism of action for pyrethrin- or pyrethroid-induced toxic effects. Anticonvulsant drugs have varying degrees of therapeutic efficacy in various animal species treated with a variety of pyrethroids, and may not be regarded as specific antidotes for pyrethroid poisoning in general (Vijverberg and van den Bercken 1990). Muscle relaxants such as mephenesin and methocarbamol may be more effective counters to pyrethroid poisoning, but appear to be more effective against Type II than Type I pyrethroids (Bradbury et al. 1981; Hiromori et al. 1986). Atropine appears to be effective in reducing pyrethroid-induced effects such as salivation and choreoathetosis in animals (Ray and Cremer 1979). Agents such as ivermectin and pentobarbitone, which act as agonists at chloride channels, have been shown to reduce salivation and choreoathetosis, respectively, in animals (Forshaw and Ray 1997). Dermal applications of Vitamin E and local anesthetic creams have effectively reduced symptoms of paresthesia following dermal exposure to pyrethroids (Flannigan et al. 1985b; Malley et al. 1985; Tucker et al. 1984).

3.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of pyrethrins and pyrethroids is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of pyrethrins and pyrethroids.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Pyrethrins and Pyrethroids

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to pyrethrins and pyrethroids are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of pyrethrins and pyrethroids. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Available data regarding health effects in humans exposed to pyrethrins or pyrethroids largely concern occupational exposure during crop applications in which exposure was considered to have occurred primarily via dermal contact, although inhalation exposure could not be ruled out. Therefore, Figure 3-4 indicates that information exists for both inhalation and dermal exposure routes. A number of human cases involved intentional ingestion of pyrethroids. Both inhalation and dermal exposures were likely in

Figure 3-4. Existing Information on Health Effects of Pyrethrins and Pyrethroids

		Systemic								
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●			●	●				
Oral	●	●			●	●				
Dermal	●	●			●	●				

Human

		Systemic								
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●							
Oral	●	●	●	●	●	●	●	●	●	●
Dermal	●	●						●	●	

Animal

● Existing Studies

the few reported cases of reactive airway responses. Some occupational exposures were considered to have been of intermediate or chronic duration due to repeated exposures ranging from weeks to years. However, observed health effects following repeated exposure to pyrethrins or pyrethroids were similar to those that characterize acute pyrethroid poisoning.

The database for health effects following oral exposure to pyrethrins or pyrethroids in experimental animals is substantial. However, as can be seen in Figure 3-4, information regarding health effects following inhalation or dermal exposure is more limited. The nervous system appears to be the predominant target of pyrethrin- and pyrethroid-induced toxicity. Genotoxicity data on pyrethrins and pyrethroids are available from studies *in vivo* and *in vitro*. Available cancer bioassays in laboratory animals exposed by the oral route indicate that pyrethrins and pyrethroids do not appear to be carcinogenic.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Reports in which inhalation could be considered to be a significant route of exposure to pyrethrins or pyrethroids are mainly available from studies of workers involved in the manufacture or use of the chemicals (Chen et al. 1991; Flannigan and Tucker 1985; Flannigan et al. 1985b; He et al. 1988, 1989, 1991; Knox et al. 1984; Kolmodin-Hedman et al. 1982; LeQuesne and Maxwell 1980; Moretto 1991; Shujie et al. 1988; Tucker and Flannigan 1983; Zhang et al. 1991). Limitations associated with these reports include lack of quantitative exposure data, lack of data on duration of exposure, and the possibility of multiple routes of exposure (i.e., dermal as well as inhalation). Dermal exposure was considered to have been the principal exposure route among individuals involved with spraying pyrethroids. A limited report in which inhalation exposure was considered to be the primary exposure route did not include exposure levels (Lessenger 1992). Limited animal inhalation toxicity data are available for pyrethrins and pyrethroids (Curry and Bennett 1985; Flucke and Thyssen 1980; Hext 1987; Kavlock et al. 1979; Miyamoto 1976; Pauluhn and Thyssen 1982; Schoenig 1995), but these studies mainly concerned lethality or used exposure levels at which serious neurological effects were elicited. Due to the limited nature of the human and animal data, an acute inhalation MRL could not be derived. Additional peer-reviewed animal studies designed to examine the effects of acute inhalation exposure to pyrethrins and pyrethroids would strengthen the database of currently available information.

The nervous system is the major target of pyrethrin- and pyrethroid-induced toxicity. Numerous reports describe clinical signs of neurotoxicity in humans (Gotoh et al. 1998; He et al. 1989; Peter et al. 1996) and laboratory animals (Eriksson and Nordberg 1990; Hudson et al. 1986; Parker et al. 1983, 1984a, 1984b, 1985; Ray and Cremer 1979; Southwood 1984) following acute oral exposure to high doses of pyrethrins or pyrethroids. Recent studies have shown neurological effects in adult mice that had been administered acute oral doses of pyrethroids during critical stages of neonatal brain growth (postpartum days 10–16) at exposure levels much lower than those eliciting the classical clinical signs of neurotoxicity (Ahlbom et al. 1994; Eriksson and Fredriksson 1991; Eriksson and Nordberg 1990; Talts et al. 1998a). The studies of Eriksson and coworkers were used as the basis for the derivation of acute MRLs for bioallethrin and deltamethrin. Additional studies designed to assess developmental neurotoxic effects at relatively low levels of oral exposure to pyrethrins and pyrethroids could serve to support or refute the findings of Eriksson and coworkers.

Paresthesia (an abnormal cutaneous sensation sometimes described as tingling, burning, stinging, numbness, and itching) has been widely reported by individuals occupationally exposed to pyrethroids (Flannigan and Tucker 1985; Flannigan et al. 1985b; Knox et al. 1984; LeQuesne and Maxwell 1980; Tucker and Flannigan 1983). Higher levels of exposure to various pyrethroids have resulted in mild acute pyrethroid poisoning that included dizziness, headache, and nausea (Chen et al. 1991; Moretto 1991; Shujie et al. 1988; Zhang et al. 1991). However, human studies typically involved the potential for multiple exposure routes and exposure levels were not quantified. Limited available peer-reviewed animal data indicate neurotoxicity following acute dermal exposure to pyrethroids (El-Elaimy 1986; Meyer 1999; Mitchell et al. 1988). Analysis of additional existing information from the pesticide industry, but not currently available to ATSDR, might preclude the need for certain additional animal studies regarding the toxic effects of acute dermal exposure to pyrethrins and pyrethroids.

Intermediate-Duration Exposure. Available reports of toxicoses in humans occupationally exposed to pyrethrins or pyrethroids include multiple exposure routes (dermal, inhalation, and possible oral) and lack quantitative exposure data. Oral data and limited inhalation data were available for laboratory animals repeatedly exposed to pyrethrins or pyrethroids (Cabral and Galendo 1990; DOD 1977; Flucke and Schilde 1980; Hext et al. 1986; IRIS 2001a, 2001b; Ishmael and Litchfield 1988; Miyamoto 1976; Mohan et al. 1998; Parker et al. 1984a, 1984b; Schoenig 1995), but there were few indications that repeated or continuous exposure result in cumulative neurological effects in animals exposed as adults. Intermediate-duration inhalation and oral MRLs were not derived for pyrethrins or pyrethroids because serious neurological effects were associated with exposure, and the lowest oral exposure levels at which these effects were seen were higher than those eliciting more subtle neurological effects following acute exposure. Existing information from the pesticide industry, but not currently available to ATSDR, should be reviewed in the process of assessing the need for additional studies.

Chronic-Duration Exposure and Cancer. Available reports of toxicity in humans occupationally exposed to pyrethrins or pyrethroids include multiple exposure routes (dermal, inhalation, and possible oral) and lack quantitative exposure data. Oral data were available for laboratory animals chronically exposed to pyrethrins or pyrethroids (Cabral and Galendo 1990; Hext et al. 1986; IRIS 2001a, 2001b; Ishmael and Litchfield 1988; Parker et al. 1984a; Schoenig 1995), but there were no indications that repeated or continuous exposure might result in cumulative neurological effects. Chronic inhalation and oral MRLs were not derived for pyrethrins or pyrethroids because LOAELs were associated with serious neurological effects, and the lowest oral exposure levels at which these effects were seen were higher than those eliciting more subtle neurological effects following acute exposure. Available cancer bioassays of animals, administered pyrethrins or selected pyrethroids orally, provide little indication of a carcinogenic effect (Cabral and Galendo 1990; Ishmael and Litchfield 1988; Miyamoto 1976; Parker et al. 1983, 1984a; Schoenig 1995). Existing information from the pesticide industry, but not currently available to ATSDR, should be reviewed in the process of assessing the need for additional studies.

Genotoxicity. No information was located regarding the genotoxicity of pyrethrins or pyrethroids in humans. Limited information indicated that pyrethrins were not mutagenic in bacterial test systems *in vitro* (see Table 3-2). Type I and Type II pyrethroids generally tested negative for mutagenicity in prokaryotic test systems, but some positive results were obtained for mutation in yeast cells exposed to selected Type I and Type II pyrethroids (see Tables 3-5 and 3-6). Tests in mammalian systems, both *in vivo* and *in vitro*, indicated that Type I and Type II pyrethroids had the potential to induce chromosomal damage (see Tables 3-5 and 3-6).

Reproductive Toxicity. No information was located regarding pyrethrin- or pyrethroid-induced reproductive toxicity in humans. Reproductive toxicity was not observed in rats administered oral doses of pyrethrins in the diet at concentrations resulting in average daily doses of 240 mg/kg for 2 generations (Schoenig 1995). One 3-generation study found no evidence for reproductive toxicity from fenpropathrin at an oral dose level of 25 mg/kg/day (Hend et al. 1979). However, recent studies indicated that intermediate-duration oral exposure of male rats to deltamethrin at a dose level of 1 mg/kg/day resulted in significantly reduced fertility (Abd El-Aziz et al. 1994). Additional reproductive toxicity studies could be designed to support or refute these results.

Developmental Toxicity. No information was located regarding pyrethrin- or pyrethroid-induced developmental toxicity in humans. Most available developmental toxicity studies in animals do not indicate that pyrethrins or pyrethroids might be considered to be developmental toxicity hazards. The World Health Organization (WHO 2001), and EPA (IRIS 2001e) reviewed a number of unpublished or proprietary developmental toxicity studies performed for various chemical organizations. Although these studies are not currently available to ATSDR, the summaries of WHO (2001) and EPA (IRIS 2001e) indicate that classical developmental effects are not elicited following exposure to pyrethroids.

Recent studies by Eriksson and coworkers indicate that exposure to pyrethroids during neonatal stages of development when the brain is rapidly growing, may result in adverse neurological effects (changes in MACh receptor density in the cerebral cortex and increased spontaneous locomotor behavior) that are not apparent until adulthood (Ahlbom et al. 1994; Eriksson and Fredriksson 1991; Eriksson and Nordberg 1990; Talts et al. 1998a). Furthermore, these effects occur at exposure levels much lower than those eliciting clinical signs of neurotoxicity in animals first exposed to pyrethroids as adults.

Immunotoxicity. A few cases of hypersensitive responses in humans exposed to pyrethrins and pyrethroids have been documented in available literature (Box and Lee 1996; Carlson and Villaveces 1977; Wagner 2000; Wax and Hoffman 1994). Available information regarding immunotoxicity in animals was limited to oral studies in which administration of selected pyrethroids resulted in immunotoxic effects such as suppression of the humoral immune response, alterations in lymphocytes, leukopenia, altered killer cell activity, and decreased spleen weight (Blaylock et al. 1995; Demian 1998; Demian and El-Sayed 1993; Dési et al. 1986; Lukowicz-Ratajczak and Krechniak 1992; Varshneya et al. 1992). No adequate studies are available in humans to assess the immunotoxic potential of pyrethrins or pyrethroids. Studies measuring specific immunologic parameters in occupationally exposed populations might provide useful information. However, inherent variation among human subjects would necessitate very large sample sizes. Animal studies designed to investigate the mechanism for pyrethroid-induced immunotoxicity might help to identify special populations at risk for such effects.

Neurotoxicity. Abundant human data show that exposure to large amounts of pyrethroids, either by accidental or intentional ingestion or by dermal and inhalation exposure during unprotected handling or spraying of pyrethroids, may result in clinical signs of neurotoxicity (Chen et al. 1991; Flannigan and Tucker 1985; Flannigan et al. 1985b; Gotoh et al. 1998; He et al. 1989, 1991; Knox et al. 1984; LeQuesne and Maxwell 1980; Moretto 1991; Peter et al. 1996; Shujie et al. 1988; Tucker and Flannigan 1983; Zhang et al. 1991). Exposure of laboratory rodents to selected Type I and Type II pyrethroids has been shown to trigger typical signs of Type I (aggressive behavior and increased sensitivity to external stimuli, fine tremor, prostration with coarse whole body tremor, elevated body temperature, and coma) and Type II (pawing and burrowing behavior, profuse salivation, increased startle response, abnormal hind limb movements, and choreoathetosis) pyrethroid poisoning. Although the majority of animal studies reporting neurotoxic effects employed oral exposure (Eriksson and Nordberg 1990; Hudson et al. 1986; Parker et al. 1983, 1984a, 1984b, 1985; Ray and Cremer 1979; Southwood 1984), these effects were also elicited following inhalation and dermal exposure (Curry and Bennett 1985; El-Elaimy 1986; Pauluhn and Thyssen 1982; Schoenig 1995). Several investigators reported typical signs of Type I or Type II pyrethroid poisoning in laboratory rodents during repeated oral administration of pyrethrins or pyrethroids (from 2 days to 2 years), but there were few indications that repeated or continuous exposure might result in cumulative neurological effects (Cabral and Galendo 1990; DOD 1977; Flucke and Schilde 1980; Hext et al. 1986; IRIS 2001a, 2001b; Ishmael and Litchfield 1988; Mohan et al. 1998; Parker et al. 1984a, 1984b; Schoenig 1995). Some investigators have reported signs of neurotoxicity such as altered locomotor activity, altered acoustic startle response, decreased active avoidance response, and changes in brain neurotransmitter concentrations at pyrethroid exposure levels below those eliciting clinical signs of Type I or Type II pyrethroid poisoning (Crofton and Reiter 1988; Hijzen et al. 1988; Husain et al. 1991; Mandhane and Chopde 1997; Mitchell et al. 1988; Moniz et al. 1994; Spinosa et al. 1999). Additional studies of the neurotoxicity of pyrethrins and pyrethroids should assess sensory function in humans and sensitivity of unique populations such as farm workers, children of farm workers, and the elderly.

Epidemiological and Human Dosimetry Studies. Available information regarding the health effects of pyrethrins and pyrethroids in humans mainly concerns reports of neurological effects following accidental or intentional ingestion or during unprotected handling or spraying (Chen et al. 1991; Flannigan and Tucker 1985; Flannigan et al. 1985b; Gotoh et al. 1998; He et al. 1989, 1991; Knox et al. 1984; LeQuesne and Maxwell 1980; Moretto 1991; Peter et al. 1996; Shujie et al. 1988; Tucker and Flannigan 1983; Zhang et al. 1991). Occupational exposure to pyrethrins and pyrethroids may be confounded by differences in specific formulations and by concurrent exposures to other pesticides. Pesticide applicators, farm workers, individuals involved in production of pyrethrins or pyrethroids, and individuals exposed in recently sprayed homes or offices might serve as a focus for well-designed epidemiological studies for further assessment of neurological effects of pyrethrins and pyrethroids, as well as assessment of other potential adverse effects, such as immunotoxicity. Studies of dosimetry would be useful in future epidemiological studies.

Biomarkers of Exposure and Effect.

Exposure. Measurement of urinary metabolites of pyrethroids can serve as useful markers of exposure (Aprea et al. 1997; Kühn et al. 1999; Leng et al. 1996, 1997a, 1997b). However, there is insufficient information from studies in humans or animals to allow for correlation of the amounts of metabolites measured in the urine to the body burden of pyrethroids or to the level of exposure to pyrethroids. Additional information regarding the relationship of urinary pyrethroid metabolite levels to pyrethroid body burden and to exposure levels could improve the ability to monitor worker's exposure to pyrethroids. Also, residues of pyrethrins and pyrethroids and their metabolites should be determined in blood of humans (antemortem) and in blood, digestive tract contents, liver, kidney, and brain of animals and accidently exposed or suicide victims (postmortem). Without detailed knowledge regarding the appearance and disappearance of parent compounds and metabolites over the course of a toxicosis, confirmed diagnoses will remain elusive to impossible.

Effect. Biomarkers of effect for pyrethrins and pyrethriods include typical neurotoxic signs of acute pyrethroid poisoning (Coats 1990; Verschoyle and Aldridge 1980). Although these clinical signs are distinctive, they are not totally unique to pyrethrin or pyrethroid poisoning.

Absorption, Distribution, Metabolism, and Excretion. The absorption, distribution, metabolism, and excretion of pyrethrins or pyrethroids following exposure by any route are not well characterized in humans. While many studies have investigated these processes for pyrethroids in various laboratory animals, in general, toxicokinetics of these compounds are not well defined. No PBPK models of pyrethrins or pyrethroids have been reported. Information to support the development of a PBPK model for pyrethrins or pyrethroids has not been systematically compiled and is currently insufficient to support such models (e.g., mechanisms and kinetic constants and variables of metabolism, tissue partition coefficients). Such models would be useful for predicting body burdens and, if combined with dose-response models, for predicting health effects of pyrethrins and pyrethroids associated with known or projected exposures.

Absorption. Although results of studies in humans and laboratory animals demonstrate that pyrethroids are absorbed following exposure by the inhaled, oral, and dermal routes, further studies would be helpful for quantifying the absorption and time-course of absorption by each exposure route. It has been proposed that pyrethroids are stored in the skin following dermal exposure and are slowly released into the systemic circulation (Eadsforth et al. 1988; Woollen et al. 1992). Given the importance of the dermal route in occupational exposure to pyrethroids, additional information regarding the time-course of absorption following dermal exposure would be helpful. There is no information available on how such factors as diet, age, sex, or other chemicals and drugs may affect the absorption of pyrethroids by any route in humans and animals. Further studies are needed to examine these factors and define potential differences in absorption over a range of pyrethrins and pyrethroids.

Distribution. The distribution of pyrethrins and pyrethroids in humans and animals has not been well studied. From the results of studies in laboratory animals, it is concluded that pyrethroids are rapidly and widely distributed and are concentrated in central and peripheral nerve tissues (Anadón et al. 1991a, 1991b, 1996; Gray and Rickard 1982; Gray et al. 1980). Additional investigations on distribution would provide a further understanding of the extent of distribution of pyrethroids to nervous system tissues (a principal target of pyrethroid toxicity) and to define the time-course for distribution and tissue retention, particularly in tissues that are targets for toxicity. Extremely limited information is available regarding distribution of pyrethroids to the fetus and into breast milk. Additional studies are needed to assess the potential risks of exposure *in utero* and via breast milk. Additional studies also may be warranted to identify factors that may alter distribution of pyrethroids and to define potential differences in distribution with respect to age and sex.

Metabolism. The metabolism of pyrethrins and pyrethroids in humans has not been well defined. Although the metabolism of pyrethroids has been extensively studied in laboratory animals, the specific enzymes responsible for the biotransformation of pyrethroids have not been identified. Further research identifying these enzymes would allow the evaluation of many potential factors, such as age, sex, and other chemicals and drugs, that could alter the metabolism of pyrethroids. This is of particular importance since metabolism of pyrethroids is generally accepted as the primary detoxifying mechanism in mammals (Gray and Soderlund 1985; Hutson 1979).

Elimination and Excretion. The elimination and excretion of pyrethrins and pyrethroids in humans have not been well defined and information is limited to studies investigating the elimination of pyrethroids from the plasma and excretion of pyrethroids into the urine. Additional information on nonurinary excretory routes and information to quantify excretion by each route in humans would be helpful for predicting routes and elimination kinetics in humans. Based on the limited information available in humans, it is not possible to predict precisely how long pyrethroids will remain in the body following exposure by various routes. Further study on the elimination kinetics of a range of pyrethroids by each route of exposure would be helpful for developing predictive models in humans. There is little information available regarding the mechanisms of excretion in either humans or animals. Further study on these mechanisms would allow assessment of the many potential factors, such as age, sex, and other chemicals and drugs, that could alter the elimination and excretion of pyrethroids.

Comparative Toxicokinetics. Insufficient information is available regarding comparative toxicokinetics of pyrethrins or pyrethroids in humans and laboratory animals. Further investigations on potential differences in humans and animals may help to determine appropriate species and strains of animals to use in predicting the toxicokinetics of pyrethroids in humans. Evaluation of mechanisms, character, and extent of human variability in the disposition of pyrethroids is also warranted.

Methods for Reducing Toxic Effects. Other than general guidelines of washing the skin with soap and water following dermal exposure and use of gastric lavage and activated charcoal following oral exposure, little additional information is available regarding methods for reducing absorption of pyrethroids. Additional studies on factors that could affect the absorption and metabolism of pyrethroids, such as diet and concomitant exposure to other chemicals and drugs, would be helpful in understanding the impact of these factors on risks from occupational exposures.

Children's Susceptibility. Neurotoxic effects have been well-characterized in humans exposed to pyrethrins and pyrethroids. Information mainly derives from individuals occupationally exposed during spraying. No reports on exposed children were found, but it is reasonable to assume that children would exhibit signs and symptoms similar to those in adults under similar exposure conditions. No information was located regarding developmental toxicity in humans exposed to pyrethrins or pyrethroids. Studies in animals have shown that neonatal exposure to pyrethroids can result in neurological effects first observed in adulthood (Ahlbom et al. 1994; Eriksson and Fredriksson 1991; Eriksson and Nordberg 1990; Talts et al. 1998a). Research efforts should focus on possible mechanisms responsible for such long-lasting postexposure effects.

No human data were located regarding age-related differences in the pharmacokinetics of pyrethrins or pyrethroids. Limited animal data suggest that young animals may be more susceptible to pyrethroid poisoning, possibly due to less efficient production of enzymes responsible for detoxification (Cantalamessa 1993).

Extremely limited data suggest that pyrethroids may be minimally transferred across the placenta to the fetus (Quistad et al. 1982). Very low levels of pyrethroids have been measured in the milk of lactating cows and goats (Gaughan et al. 1978; Hunt and Gilbert 1977; Quistad et al.1982; Ridlen et al. 1984; Wszolek et al. 1980).

No data were located regarding pediatric-specific methods to reduce peak absorption of pyrethrins or pyrethroids following exposure, to reduce body burdens, or to interfere with mechanisms of action. Based on available information, it is reasonable to assume that methods recommended for treating adults will also be applicable to children.

Child health data needs relating to exposure are discussed in Section 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

The Federal Research In Progress database (FEDRIP 2001) lists an ongoing study in which Dr. B. Wilson, from the University of California, Davis, California has proposed the development of biomarkers of exposure and effect for organophosphorus and pyrethroid insecticidal sprays. Two studies were located in the Computer Retrieval of Information in Scientific Projects database (CRISP 2001). Dr. S. Holladay, from Virginia Polytechnic Institute and State University, Blacksburg, Virginia, is investigating the immunotoxicity of permethrin. Dr. D. Soderlund, from Cornell University, Ithaca, New York, is investigating specific mechanisms of action of pyrethroids in vertebrate systems.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

The naturally-occurring pyrethrins, extracted from chrysanthemum flowers, are esters of chrysanthemic acid (Pyrethrin I, Cinerin I, and Jasmolin I) and esters of pyrethric acid (Pyrethrin II, Cinerin II, and Jasmolin II). In the United States, the pyrethrum extract is standardized as 45–55% w/w total pyrethrins. The typical proportion of Pyrethrins I to II is 0.2:2.8, while the ratio of pyrethrins:cinerins:jasmolins is 71:21:7 (Tomlin 1997). Information regarding the chemical identity of the pyrethrins is presented in Table 4-1.

Pyrethroids are synthetic esters derived from the naturally-occurring pyrethrins. One exception to the axiom that all pyrethroids are esters of carboxylic acids is noteworthy. There is a group of oxime ethers that exhibits insecticidal activity similar in nature to the pyrethrins and pyrethroid esters (Davies 1985). Little data exist regarding these compounds; and no commercial products have been produced. Commercially available pyrethroids include allethrin, bifenthrin, bioresmethrin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, esfenvalerate (fenvalerate), flucythrinate, flumethrin, fluvalinate, fenpropathrin, permethrin, phenothrin, resmethrin, tefluthrin, tetramethrin, and tralomethrin. Information regarding the chemical identity of pyrethroids is shown in Table 4-2.

With the exception of deltamethrin, pyrethroids are a complex mixture of isomers rather than one single pure compound. For pyrethroids possessing the cyclopropane moiety, isomerism about the cyclopropane ring greatly influences the toxicity of these insecticides. The presence of two chiral centers in the ring results in two pairs of diastereomers. The diastereomers and their nonsuperimposable mirror images (enantiomers) are illustrated in Figure 4-1. In this figure, the C-1 position of the ring is assigned to the carbon atom bonded to the ester moiety. It is also customary to designate the stereochemistry at the C-3 position as simply cis or trans relative to the ester group bonded to C-1 rather than assigning its absolute configuration. The 1R conformations about the cyclopropane ring are considerably more toxic than the 1S isomers. Both the cis and trans isomers show insecticidal activity, but have differing mammalian toxicities, with the cis isomers being more potent (Ray 1991). Pyrethroids that contain a cyano substituent at the alcohol moiety (Type II pyrethroids) demonstrate differing toxicity based upon the optical isomerism of the alpha carbon. It has been demonstrated that the S conformation about the alpha carbon is considerably more toxic towards insects when compared to the R conformation (Dorman and

Table 4-1. Chemical Identity of the Pyrethrins

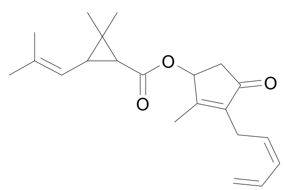
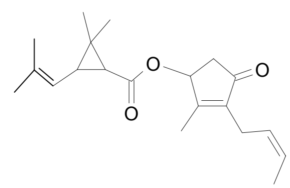
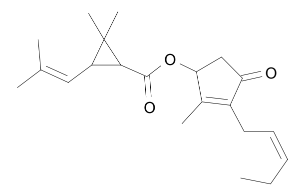
Characteristic	Pyrethrin I	Cinerin I	Jasmolin I
Synonym(s)[b]	(Z)-(S)-2-methyl-4-oxo-3-(penta-2,4-dienyl)cyclo pent-2-enyl (1R)-trans-2,2-dimethyl-3-(2-methyl prop-1-enyl)cyclo-propanecarboxylate	(Z)-(S)-3-(but-2-enyl)-2-methyl-4-oxocyclopent-2-enyl (1R)-trans-2,2-di methyl-3-(2-methyl prop-1-enyl)-cyclopropanecarboxylate	(Z)-(S)-2-methyl-4-oxo-3-(pent-2-enyl)cyclopent-2-enyl (1R)-trans-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate
Ratio of isomers	pure isomer	pure isomer	pure isomer
Registered trade name(s)	Alfadex, Evergreen, ExciteR, Milon, Pycon, Pyrocide, Pyronyl	Alfadex, Evergreen, ExciteR, Milon, Pycon, Pyrocide, Pyronyl	Alfadex, Evergreen, ExciteR, Milon, Pycon, Pyrocide, Pyronyl
Chemical formula	$C_{21}H_{28}O_3$	$C_{20}H_{28}O_3$	$C_{21}H_{30}O_3$
Chemical structure			
Identification numbers:			
CAS registry	121-21-1	25402-06-6	4466-14-2
NIOSH RTECS[c]	GZ1725000	GZ1540000	No data
EPA hazardous wasted	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	6302
HSDB[d]	6302	6837	No data
NCI	No data	No data	No data

Table 4-1. Chemical Identity of the Pyrethrins *(continued)*

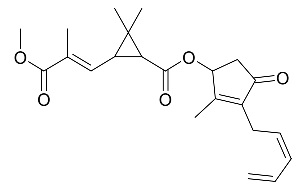
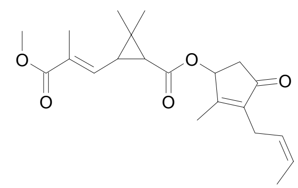
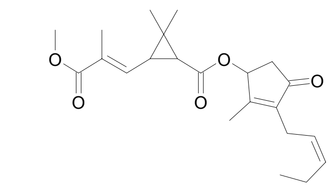
Characteristic	Pyrethrin II	Cinerin II	Jasmolin II
Synonym(s)[b]	(Z)-(S)-2-methyl-4-oxo-3-(penta-2,4-dienyl)cyclo pent-2-enyl (E)-(1R)-trans-3-(2-methoxy carbon ylprop-1-enyl)-2,2-dimethylcyclo-propanecarboxylate	(Z)-(S)-3-(but-2-enyl)-2-methyl-4-oxocyclopent-2-enyl (E)-(1R)-trans-3-(2-methoxycarbonylprop-1-enyl)-2,2-dimethyl cyclopropane-carboxylate	(Z)-(S)-2-methyl-4-oxo-3-(pent-2-enyl)cyclopent-2-enyl (E)-(1R)-trans-3-(2-methoxycarbonylprop-1-enyl)-2,2-dimethylcyclopropane-carboxylate
Ratio of isomers	pure isomer	pure isomer	pure isomer
Registered trade name(s)	Alfadex, Evergreen, ExciteR, Milon, Pycon, Pyrocide, Pyronyl	Alfadex, Evergreen, ExciteR, Milon, Pycon, Pyrocide, Pyronyl	Alfadex, Evergreen, ExciteR, Milon, Pycon, Pyrocide, Pyronyl
Chemical formula	$C_{22}H_{28}O_5$	$C_{21}H_{28}O_5$	$C_{22}H_{30}O_3$
Chemical structure			
Identification numbers:			
CAS registry	121-29-9	121-20-0	1172-63-0
NIOSH RTECS[c]	GZ0700000	No data	No data
EPA hazardous wasted	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB[d]	6303	6838	No data
NCI	No data	No data	No data

Table 4-2. Chemical Identity of Selected Pyrethroids[a]

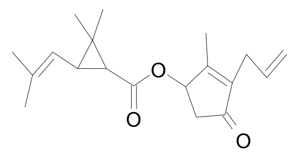
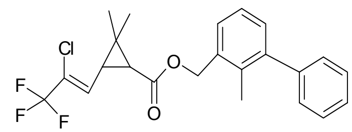
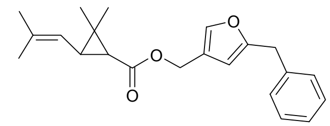
Characteristic	Allethrin	Bifenthrin	Bioresmethrin
Synonym(s)[b]	2-methyl-4-oxo-3-(2-propenyl)-2-cyclopenten-1-yl 2,2-dimethyl-3-(2-methyl-1-propenyl)cycloprane-carboxylate	(2-methyl[1,1'-biphenyl]-3-yl)methyl 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate	(1R-trans)-[5-phenylmethyl)-3-furanyl]mehtyl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropane-carboxylate
Ratio of isomers	$95% (1R)-isomers $75% trans-isomers	$97% cis-isomer	$90% (1R)-trans-isomer
Registered trade name(s)	Pyresin, Pynamin Forte, Exthrin	Talstar	Isathrine
Chemical formula	$C_{19}H_{26}O_3$	$C_{23}H_{22}ClF_3O_2$	$C_{22}H_{26}O_3$
Chemical structure			
Identification numbers:			
CAS registry	584-79-2	82657-04-3	28434-01-7
NIOSH RTECS[c]	GZ1925000	GZ1227800	GZ1227800
EPA hazardous wasted	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	NA2902, NA2588, UN2588, UN2902, UN2903, UN3201, IMO3.2, IMO6.1	No data	No data
HSDB[d]	1511	6568	6568
NCI	No data	No data	No data

Table 4-2. Chemical Identity of Selected Pyrethroids[a] *(continued)*

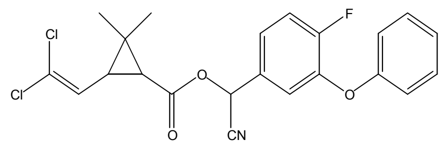
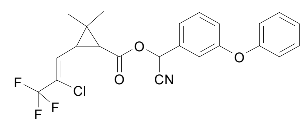
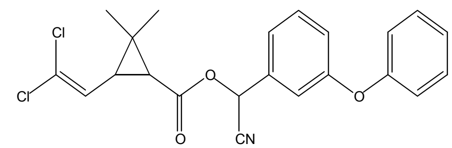
Characteristic	Cyfluthrin	Cyhalothrin	Cypermethrin
Synonym(s)[b]	Cyano(4-fluoro-3-phenoxyphenyl)-methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate	[1α,3α(Z)]-(±)-cyano-(3-phenoxy-phenyl)methyl 3-(2-chloro-3,3,3-trifluoro-1-propenyl)2,2-dimethyl-cyclopropanecarboxylate	Cyano(3-phenoxyphenyl)methyl 3-(2,2-dichloro ethenyl)-2,2-dimethyl-cyclopropanecarboxylate
Ratio of isomers	unstated stereochemistry	$95% cis-isomers	unstated stereochemistry
Registered trade name(s)	Baythroid, Baygon aerosol, Solfac[b]	Cyhalon, Grenade	Arrivo, Cymbush, Cymperator, Cynoff, Ripcord, Basathrin, Demar, Grand, Starcyp[b]
Chemical formula	$C_{22}H_{18}Cl_2FNO_3$	$C_{23}H_{19}ClF_3NO_3$	$C_{22}H_{19}Br_2NO_3$
Chemical structure			
Identification numbers:			
CAS registry	68359-37-5	68085-85-8	52315-07-8
NIOSH RTECS[c]	GZ1253000	GZ122770	GZ1250000
EPA hazardous wasted	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB[d]	6599	6791	6600
NCI	No data	No data	No data

Table 4-2. Chemical Identity of Selected Pyrethroids[a] *(continued)*

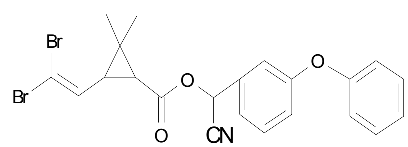
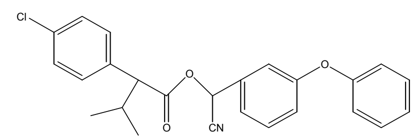
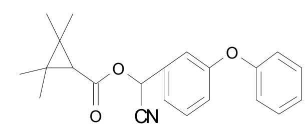
Characteristic	Deltamethrin	Esfenvalerate	Fenpropathrin
Synonym(s)[b]	[1R-[1α(S*),3α]]-Cyano (3-phenoxy-phenyl)methyl 3-(2,2-dibromo ethenyl)-2,2-dimethylcyclopropane-carboxylate, decamethrin	{S-R*,R*]-Cyano(3-phenoxyphenyl)-methyl 4-chloro-2-(1-methylethyl)-benzeneacetate, Fenvalerate	Cyano(3-phenoxyphenyl)methyl 2,2,3,3-tetramethylcyclopropane-carboxylate(racemate) Fenpropanate (unspecified)
Ratio of isomers	$98% single isomer	$75% (S,S)-isomers	unstated stereochemistry
Registered trade name(s)	Butox, Decis, K-Othrin, Kordon, Sadethrin[b]	Sumi-alfa, Sumi-alpha, Asana (esfenvalerate), Pydrin, Ectrin,Sumicidin, Arfen, Dufen, Fenval (fenvalerate)[b]	Danitol, Herald, Meothrin, Rody, Digital[b]
Chemical formula	$C_{22}H_{19}Br_2NO_3$	$C_{25}H_{22}ClNO_3$	$C_{22}H_{23}NO_3$
Chemical structure			
Identification numbers:			
CAS registry	52918-63-5	66230-04-4, 51630-58-1 (fenvalerate)	64257-84-7 (racemic), 39515-41-8 (stereochemistry)
NIOSH RTECS[c]	GZ1233000, GZ1232000	CY1576367, CY1576350	GZ2090500, GZ2090000
EPA hazardous waste	No data	CY1576350	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB[d]	6604	6625, 6640	6636
NCI	No data	No data	No data

Table 4-2. Chemical Identity of Selected Pyrethroids[a] *(continued)*

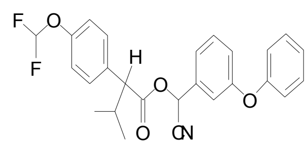
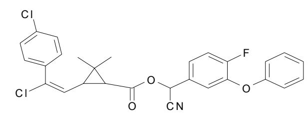
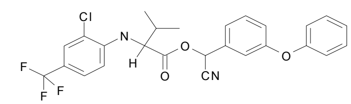
Characteristic	Flucythrinate	Flumethrin	Fluvalinate
Synonym(s) [b]	Cyano(3-phenoxyphenyl)methyl 4-(difluoromethoxy)-α-(1-methylethyl)-benzeneacetate	α-Cyano-4-fluoro-3-phenoxybenzyl 3-(ß,4-dichlorostyryl)-2,2-dimethyl-cyclopropanecarboxylate	Cyano(3-phenoxyphenyl)methyl N-N-[2-chloro-4-(trifluoromethyphenyl)-DL-valinate, D-valinate
Ratio of isomers	No data	unstated stereochemistry	tau-fluvalinate is a 1:1 mixture of (R)-a-cyano, 2-(R) and (S)-a- cyano, 2-(R) diasteriomers
Registered trade name(s)	Cybolt, Cythrin, Pay-off, Fluent	Bayticol, Bayvarol	Klartan, Mavrik
Chemical formula	$C_{26}H_{23}F_2NO_4$	$C_{28}H_{22}Cl_2FNO_3$	$C_{26}H_{22}ClF_3N_2O_3$
Chemical structure			
Identification numbers:			
CAS registry	70124-77-5	69770-45-2	69409-94-5, 102851-06-9 (tau-fluvalinate)
NIOSH RTECS[c]	CY1578620	No data	YV9397100
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB[d]	6647	No data	6659
NCI	No data	No data	No data

Table 4-2. Chemical Identity of Selected Pyrethroids[a] *(continued)*

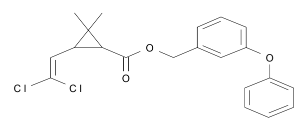
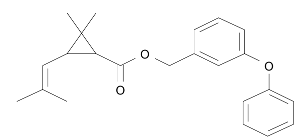
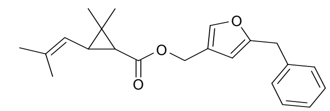
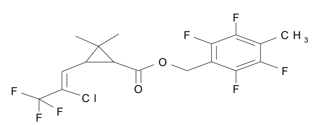
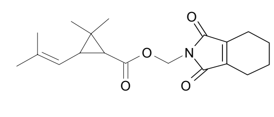
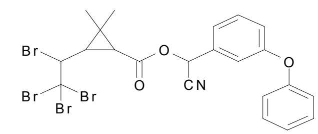
Characteristic	Permethrin	Phenothrin	Resmethrin
Synonym(s)[b]	(3-phenoxyphenyl)methyl3-(2,2-dichloroehenyl)-2,2-dimethyl-cyclopropanecarboxylate	(3-Phenoxyphenyl)methyl2,2-dimethyl-3-(2-methyl-1-propenyl)-cyclopropanecarboxylate	[5-Phenylmethyl)-3-furanyl]mehtyl 2,2-dimethyl-3-(2-methyl-1-propenyl)-cyclopropanecarboxylate
Ratio of isomers	(1R, trans):(1R,cis):(1S, trans):(1S, cis)=3:2:3:2[e]	mixed isomers	20–30% (1RS)-cis-isomers 80–70% (1(RS)-trans-isomers)
Registered trade name(s)	Ambush, Assithrin, Cliper, Coopex, Corsair, Dragnet, Dragon, Kafil, Eksmin, Perkill, Pounce	Sumithrin,	Synthrin, Chrysron
Chemical formula	$C_{21}H_{20}Cl_2O_3$	$C_{23}H_{26}O_3$	$C_{22}H_{26}O_3$
Chemical structure			
Identification numbers:			
CAS registry	52645-53-1	26002-80-2	10453-86-8
NIOSH RTECS[c]	GZ1255000	GZ1975000	GZ1310000
EPA hazardous wasted	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB[d]	6740	3922	6790
NCI	No data	No data	No data

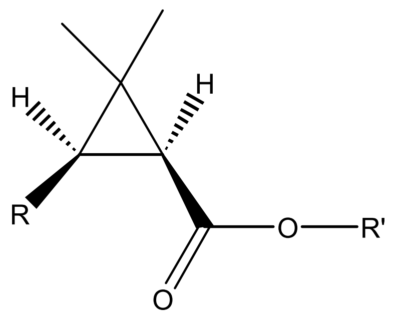
Table 4-2. Chemical Identity of Selected Pyrethroids[a] *(continued)*

Characteristic	Tefluthrin	Tetramethrin	Tralomethrin
Synonym(s) [b]	[1α,3α(Z)]-(±)-(2,3,5,6-tetrafluoro-4-methylphenyl)methyl 3-(2-chloro-3,3,3-trifluoro-1propenyl)-2,2-dimethylcyclopropanecarboxylate	(1,3,4,5,6,7-Hexahydro-1,3-dioxo-2H-isoindol-2-yl)methyl 2,2-dimethyl-3-(2-methyl-1-propenyl)-cyclopropanecarboxylate	Cyano(3-phenoxyphenyl)methyl 2,2-dimethyl-3-(1,2,2,2-tetrabromoethyl)-cyclopropanecarboxylate
Ratio of isomers	mixture of isomers	(1R, trans):(1R,cis):(1S, trans):(1S, cis)=4:1:4:1[e]	unstated stereochemistry
Registered trade name(s)	Force, Fireban	Neo-Pynamin, Duracide	Saga, Scout, Tralox, Tracker, Tralate
Chemical formula	$C_{17}H_{14}ClF_7O_2$	$C_{19}H_{25}NO_4$	$C_{22}H_{19}Br_4NO_3$
Chemical structure			
Identification numbers:			
CAS registry	79538-32-2	7696-12-0	66841-25-6
NIOSH RTECS[c]	GZ1227850	GX1730000	GZ2009500
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB[d]	No data	6738	6604
NCI	No data	No data	No data

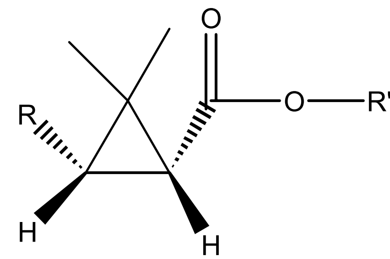
[a]All information obtained from Tomlin, 1997 except where noted.
[b]Chemical names used are those currently indexed by the Chemical Abstracts Service.
[c]NIOSH 1987
[d]HSDB 2001
[e] WHO 2001

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS =Registry of Toxic Effects of Chemical Substances

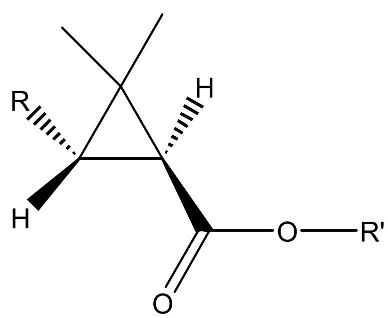
Figure 4-1. Four Possible Isomers of Type I Pyrethroids



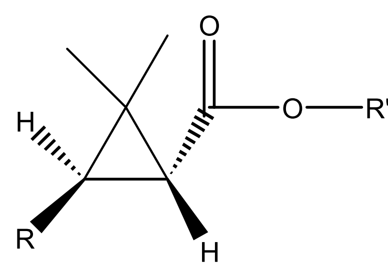
1S *cis* configuration



1R *cis* configuration



1S *trans* configuration



1R *trans* configuration

Beasley 1991). Figure 4-2 illustrates the S conformation of the type II pyrethroid cyhalothrin about the alpha carbon. Pyrethroids such as cyfluthrin, cypermethrin, and cyhalothrin possess three chiral centers, and thus consist of eight possible isomers. The production of pyrethroids with differing isomeric ratios is one reason for the wide variation in reported toxicities of these compounds. For example, cypermethrin is formulated as four different insecticides (alpha-, beta-, theta- and zeta-cypermethrin) depending upon the ratio of the different isomers; and each of these products have different toxicologic properties. The complex compositions of several important pyrethroids are illustrated in Table 4-3.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of the pyrethrins and selected pyrethroids are located in Tables 4-4 and 4-5, respectively. Generally, pyrethrins and pyrethroids have low vapor pressures, low Henry's law constants, and large octanol/water coefficients (K_{ow}), and are not very soluble in water. Aside from their interaction with polarized light, enantiomers possess identical physical properties (e.g., boiling point, melting point, solubility, etc.). Diastereomers have different physical properties however, and changes in the geometrical isomeric composition can lead to different values in the properties reported for the pyrethroids listed in Table 4-5.

Figure 4-2. Illustration of the S Conformer about the Alpha Carbon for the Type II Pyrethroid Cyhalothrin

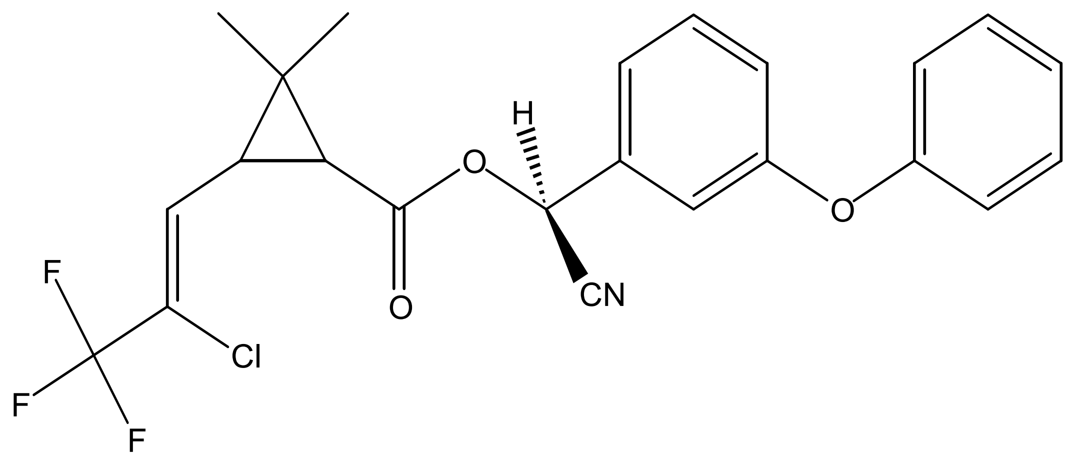


Table 4-3. Stereoisomers of Selected Pyrethroids[a]

Pyrethroid	Different products	Isomer composition
Cypermethrin	alpha-cypermethrin	Racemic mixture comprised of: (S)-alpha-cyano-3-phenoxybenzyl-(1R)-cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-carboxylate and (R)-alpha-cyano-3-phenoxybenzyl-(1S)-cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate
	beta-cypermethrin	Mixture comprised of two enantiomeric pairs in a 2:3 ratio: (S)-alpha-cyano-3-phenoxybenzyl-(1R)-cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-carboxylate and (R)-alpha-cyano-3-phenoxybenzyl-(1S)-cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate with (S)-alpha-cyano-3-phenoxybenzyl-(1R)-trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (R)-alpha-cyano-3-phenoxybenzyl-(1S)-trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate
	theta-cypermethrin	Racemic mixture comprised of: (S)-alpha-cyano-3-phenoxybenzyl-(1R)-trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclo-propanecarboxylate and (R)-alpha-cyano-3-phenoxybenzyl-(1S)-trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate
	zeta-cypermethrin	Mixture of the stereoisomers: (S)-alpha-cyano-3-phenoxybenzyl(1RS,3RS;1RS,3SR)-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropanecarboxylate where the ratio of the (S); (1RS,3RS) isomeric pair to the (S);(1RS,3SR) isomeric pair lies in the range of 45-55 to 55-45.

Table 4-3. Stereoisomers of Selected Pyrethroids[a] *(continued)*

Pyrethroid	Different products	Isomer composition
Cyfluthrin	cyfluthrin	Comprised of a mixture of the 4 diastereomeric pairs of enantiomers: **I** = (R)-alpha-cyano-4-fluoro-3-phenoxybenzyl-(1R)-cis -3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropanecarboxylate + (S)-alpha, (1S)-cis **II** = (S)-alpha-cyano-4-fluoro-3-phenoxybenzyl-(1R)-cis -3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropanecarboxylate + (R)-alpha, (1S)-cis **III** = (R)-alpha-cyano-4-fluoro-3-phenoxybenzyl-(1R)-trans -3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate + (S)-alpha, (1S)-trans IV = (S)-alpha-cyano-4-fluoro-3-phenoxybenzyl-(1R)-trans -3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate + (R)-alpha, (1S)-trans The technical grade product consists of 23-26% **I**, 16-19% **II**, 33-36% **III** and 22-25% IV.
	beta-cyfluthrin	Mixture of **II** and IV in a 1:2 ratio.
Cyhalothrin	cyhalothrin	(RS)-alpha-cyano-3-phenoxybenzyl (Z) (1RS)-cis-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate
	lambda-cyhalothrin	Racemic mixture comprised of: (S)-alpha-cyano-3-phenoxybenzyl (Z) (1R)-cis-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate and (R)-alpha-cyano-3-phenoxybenzyl (Z) (1S)-cis-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate

[a]All information obtained from Tomlin 1997

Table 4-4. Physical and Chemical Properties of Pyrethrins[a]

Property	Pyrethrin I	Cinerin I	Jasmolin I
Molecular weight	328.5	316.4	330.5
Color	No data	No data	No data
Physical state	Viscous liquid[b]	No data	No data
Melting point, EC	No data	No data	No data
Boiling point, EC	146–150 at 0.0005 mm Hg, 170 at 0.1 mm Hg[c]	136–138 at 0.008 mm Hg[d]	No data
Density, g/cm^3 at 25 EC	1.51 (18°C)	No data	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water, mg/L	0.2	Insoluble	0.03[i]
Organic solvent(s)	Soluble	Soluble	No data
Partition coefficients:			
Log K_{ow}	5.9	5.93[i]	6.42[i]
Vapor pressure, mm Hg at 25 EC	2.03×10^{-5}	1.1×10^{-6}[i]	4.8×10^{-7}[i]
Henry's law constant, atm-m^3/mol at 25 EC	7.7×10^{-7}[i]	9.6×10^{-7}[i]	1.3×10^{-6}[i]
Autoignition temperature	No data	No data	No data
Flashpoint, EC (Pensky-Martens closed cup)	No data	No data	No data
Flammability limits, EC	No data	No data	No data
Conversion factors			
Air (25 EC1)[e]	1 mg/m^3=0.074 ppm	1 mg/m^3=0.077 ppm	1 mg/m^3=0.074 ppm
Explosive limits	No data	No data	No data

Table 4-4. Physical and Chemical Properties of Pyrethrins[a] *(continued)*

Property	Pyrethrin II	Cinerin II	Jasmolin II
Molecular weight	372.5	360.4	357.7
Color	No data	No data	No data
Physical state	Viscous liquid[b]	Viscous oil[b]	No data
Melting point, EC	No data	No data	No data
Boiling point, EC	192–193 at 0.007 mm Hg, 200 at 0.1 mm Hg[c]	182–184 at 0.001 mm Hg	No data
Density, g/cm^3 at 25 EC	No data	No data	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water, mg/L	9.0	Insoluble	0.09[i]
Organic solvent(s)	Soluble	Soluble	No data
Partition coefficients:			
Log K_{ow}	4.3	4.98[i]	5.47[i]
Vapor pressure, mm Hg at 25 EC	3.98×10^{-7}	4.6×10^{-7}[i]	1.9×10^{-7}[i]
Henry's law constant, atm-m^3/mol at 25 EC	7.4×10^{-10}[i]	9.2×10^{-10}[i]	1.2×10^{-9}[i]
Autoignition temperature	No data	No data	No data
Flashpoint, EC (Pensky-Martens closed cup)	No data	No data	No data
Flammability limits, EC	No data	No data	No data
Conversion factors			
Air (25 EC1)[e]	1 mg/m^3=0.066 ppm	1 mg/m^3=0.068 ppm	1 mg/m^3=0.065 ppm
Explosive limits	No data	No data	No data

[a]All information obtained from HSDB, 2001 except where noted
[b]Technical grade
[c]Tomlin, 1997
[d]Budavari 1996
[g]USDA 2001a
[e]These air conversion factors were calculated by using the average molecular weight and ideal gas law.
[f]Milne 1995
[h]Howard and Meylan 1997
[i]Estimated value from EPIWIN (Syracuse Research Corporation)

dec. = decomposes

Table 4-5. Physical and Chemical Properties of Selected Pyrethroids[a]

Property	Allethrin	Bifenthrin	Bioresmethrin[b]
Molecular weight	302.4	422.9	338.4
Color	Pale yellow[b,c]	Light brown[c]	Yellow to brown[c]
Physical state	Viscous liquid	Viscous oil	Viscous liquid[c]
Melting point, EC	~4	68–70	71.5-83[d]
Boiling point, EC	281.5	No data	dec. >180
Density, g/cm^3 at 25 EC	1.01 (25 EC)	1.212 (25 EC)	1.050 (20 EC)
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water, mg/L	4.6 (25 EC)	0.1	<0.3 (25 EC)
Organic solvent(s)	Soluble	Soluble	Soluble
Partition coefficients:			
Log K_{ow}	4.8	6[e]	>4.7
Vapor pressure, mm Hg at 25 EC	$1.2x10^{-6}$ (21 EC)	$1.8x10^{-4}$[d]	$1.4x10^{-8}$
Henry's law constant, atm-m^3/mol at 25 EC	$6.1x10^{-7}$[i]	$<1.0x10^{-3}$[d]	$1.3x10^{-7}$[f]
Autoignition temperature	No data	No data	No data
Flashpoint, EC (Pensky-Martens closed cup)	87[b]	165[b]	92[b]
Flammability limits	No data	No data	No data
Conversion factors			
Air (25 EC1)[g]	1 mg/m^3=0.081 ppm	1 mg/m^3=0.058 ppm	1 mg/m^3=0.072 ppm
Explosive limits	No data	No data	No data

Table 4-5. Physical and Chemical Properties of Selected Pyrethroids[a] *(continued)*

Property	Cyfluthrin	Cyhalothrin	Cypermethrin
Molecular weight[c]	453.3	449.9	416.3
Color	Yellowish brown[c]	Yellow-brown[c]	Yellow brown[b,c]
Physical state	Oil (A)	Viscous liquid[c]	Viscous semi-solid[b,c]
Melting point, EC	60 (A)	49.2[g]	80.5
Boiling point, EC	No data	187–190	No data
Density, g/cm^3 at 25 EC	No data	1.25	1.25
Odor	Aromatic	Mild	Odorless
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water, mg/L	0.002 (20 EC)[g]	0.003 (20 EC)	0.004 (20 EC)
Organic solvent(s)	Soluble	Soluble	Soluble
Partition coefficients:			
Log K_{ow}	5.94	6.9	6.6
Vapor pressure, mm Hg at 25 EC	2.03×10^{-9}[d]	1.5×10^{-9} (20 EC)[d]	3.07×10^{-9} (20 EC)
Henry's law constant, atm-m^3/mol at 25 EC	9.5×10^{-7}[h]	1.8×10^{-7}[d]	4.2×10^{-7}[d]
Autoignition temperature	No data	No data	No data
Flashpoint, EC (Pensky-Martens closed cup)	107[b]	>100[b]	No data
Flammability limits, EC	No data	No data	No data
Conversion factors			
Air (25 EC1)[e]	1 mg/m^3=0.054 ppm	1 mg/m^3=0.054 ppm	1 mg/m^3=0.059 ppm
Explosive limits	No data	No data	No data

Table 4-5. Physical and Chemical Properties of Selected Pyrethroids[a] *(continued)*

Property	Deltamethrin	Esfenvalerate	Fenpropathrin
Molecular weight[c]	505.2	419.9	349.4
Color	Colorless	Colorless	Yellow brown[c]
Physical state	Crystals	Crystals	Solid[c]
Melting point, EC	101–102	59–60.2	45–50
Boiling point, EC	No data	151–167	No data
Density, g/cm^3 at 25 EC	0.55[b]	1.175	1.15 (25 EC)
Odor	Odorless	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water, mg/L	<0.002	0.0002 (25 EC)	0.014 (25 EC)[d]
Organic solvent(s)	Soluble	Soluble	Soluble
Partition coefficients:			
Log K_{ow}	6.1	4.0	6.0 (20 EC)
Vapor pressure, mm Hg at 25 EC	$1.5x10^{-8}$	$1.5x10^{-9}$	$5.5x10^{-6}$ (20 EC)
Henry's law constant, atm-m^3/mol at 25 EC	$1.2x10^{-4}$	$4.1x10^{-7}$[d]	$1.8x10^{-4}$[g]
Autoignition temperature	No data	No data	No data
Flashpoint, EC (Pensky-Martens closed cup)	No data	256[b]	No data
Flammability limits, EC	No data	No data	No data
Conversion factors			
Air (25 EC1)[g]	1 mg/m^3=0.048 ppm	1 mg/m^3=0.058 ppm	1 mg/m^3=0.070 ppm
Explosive limits	No data	No data	No data

Table 4-5. Physical and Chemical Properties of Selected Pyrethroids[a] *(continued)*

Property	Flucythrinate	Flumethrin[b]	Fluvalinate
Molecular weight[c]	451.5	510.4	502.9
Color	Dark amber[b,c]	Yellowish[c]	Yellow-amber[c]
Physical state	Viscous liquid[c]	Viscous oil[c]	Viscous liquid[c]
Melting point, EC	No data	No data	No data
Boiling point, EC	108 at 0.35 mm Hg	>250	>450 164 at 0.07 mm Hg[b]
Density, g/cm^3 at 25 EC	1.189 (22 EC)	No data	1.29
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water, mg/L	0.5 (21 EC)	9.7x10^{-5}[f]	0.002
Organic solvent(s)	Soluble	No data	Soluble
Partition coefficients:			
Log K_{ow}	4.7[d]	7.65[i]	4.26[g]
Vapor pressure, mm Hg at 25 EC	8.5x10^{-9}[d]	3.9x10^{-9}[f]	5.7x10^{-7}[d]
Henry's law constant, atm-m^3/mol at 25 EC	8.47x10^{-8}[d]	4.2x10^{-8}[f]	3.05x10^{-5}[d]
Autoignition temperature	No data	No data	No data
Flashpoint, EC (Pensky-Martens closed cup)	No data	No data	90[c]
Flammability limits, EC	No data	No data	No data
Conversion factors			
Air (25 EC1)[e]	1 mg/m^3=0.054 ppm	1 mg/m^3=0.048 ppm	1 mg/m^3=0.049 ppm
Explosive limits	No data	No data	No data

Table 4-5. Physical and Chemical Properties of Selected Pyrethroids[a] *(continued)*

Property	Permethrin	Phenothrin	Resmethrin
Molecular weight[c]	391.3	350.5	338.4
Color	Colorless to yellow[c]	Colorless	Colorless
Physical state	Crystals to viscous liquid[c]	Liquid	Crystals
Melting point, EC	34–35	No data	56.5
Boiling point, EC	220 @ 0.05 mm Hg[f]	>290	dec. at >180 EC
Density, g/cm^3 at 25 EC	1.19–1.27 (20 EC)	1.061	0.96-0.97 (20 EC)
Odor	No data	No data	Chrysanthemate
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water, mg/L	0.006 (20 EC)	2.0 (30 EC)	0.037 (25 EC)[b]
Organic solvent(s)	Soluble	Soluble	Soluble
Partition coefficients:			
Log K_{ow}	6.5	7.54[f]	5.43
Vapor pressure, mm Hg at 25 EC	2.2×10^{-8}	1.4×10^{-7}[b]	1.13×10^{-8}[i]
Henry's law constant, atm-m^3/mol at 25 EC	1.9×10^{-6}[d]	1.4×10^{-6}[f]	$<8.9 \times 10^{7}$[d]
Autoignition temperature	No data	No data	No data
Flashpoint, EC (Pensky-Martens closed cup)	>100[b]	107[b]	129[b]
Flammability limits, EC	No data	No data	No data
Conversion factors			
Air (25 EC1)[e]	1 mg/m^3=0.062 ppm	1 mg/m^3=0.070 ppm	1 mg/m^3=0.072 ppm
Explosive limits	No data	No data	No data

Table 4-5. Physical and Chemical Properties of Selected Pyrethroids[a] *(continued)*

Property	Tefluthrin[b]	Tetramethrin	Tralomethrin
Molecular weight	418.7	331.4	665.0
Color	Colorless	Colorless	Yellow orange
Physical state	Solid	Crystals	Resinoid
Melting point, EC	44.6	65–80	138–148
Boiling point, EC	153 at 1 mm Hg	180–190	No data
Density, g/cm^3 at 25 EC	1.48	1.1 (20 EC)	1.70 (20 EC)
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water, mg/L	0.002 (20 EC)	1.83[b]	0.08
Organic solvent(s)	Soluble	Soluble	Soluble
Partition coefficients:			
Log K_{ow}	6.5	4.6[c]	7.6[f]
Vapor pressure, mm Hg at 25 EC	6.0×10^{-5}	7.1×10^{-6}[b]	3.6×10^{-11}
Henry's law constant, atm-m^3/mol at 25 EC	4.6×10^{-4}[f]	8.3×10^{-9}[f]	3.9×10^{-15}[d]
Autoignition temperature	No data	No data	No data
Flashpoint, EC (Pensky-Martens open cup)	124	No data	No data
Flammability limits, EC	No data	No data	No data
Conversion factors			
Air (25 EC1)[g]	1 mg/m^3=0.058 ppm	1 mg/m^3=0.074 ppm	1 mg/m^3=0.074 ppm
Explosive limits	No data	No data	No data

[a]All information obtained from HSDB 2001 except where noted
[b]Tomlin 1997
[c]Technical grade
[d]USDA 2001a
[e]Milne 1995
[f]Estimated value from EPIWIN (Syracuse Research Corporation)
[g]These air conversion factors were calculated by using the average molecular weight and ideal gas law
[h]Budavari 1996
[i]Howard and Meylan 1997

dec. = decomposes

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Information regarding the manufacturers of various pyrethrins and pyrethroids in the United States is given in Table 5-1 (SRI 2000). Table 5-2 lists the number of facilities in each state that produce, process, or import pyrethrins and pyrethroids for commercial use. The intended use and the range of maximum amounts of these substances that are stored on site are also included. The data listed in these tables are derived from the Toxics Release Inventory (TRI99 2001). Only certain types of facilities were required to report, and this is not an exhaustive list. The only pyrethroids that are on the list are allethrin, bifenthrin, cyfluthrin, cyhalothrin, fenpropathrin, fluvalinate, permethrin, phenothrin, resmethrin, and tetramethrin (TRI99 2001). Furthermore, data have only been reported for bifenthrin, cyfluthrin, permethrin, resmethrin, and tetramethrin. No data regarding the production volumes are available.

Naturally-occurring pyrethrins are produced by certain species of chrysanthemum plants (*Chrysanthemum cinerariaefolium* and *Chrysanthemum cineum*). Either the flowers are dried and powdered or the oils within the flowers are extracted with solvents such as petroleum ether, acetone, or acetic acid (Metcalf 1995). Synthetic pyrethroids are manufactured by the esterification of an appropriate acid with an appropriate alcohol (Table 5-3).

5.2 IMPORT/EXPORT

No data regarding the import or export volumes of pyrethrins and pyrethroids are available.

5.3 USE

Naturally-occurring pyrethrins were first used around 1800 in the Transcaucasus region of Asia to control human lice, mosquitoes, cockroaches, beetles, and flies. Pyrethroids are broad-spectrum insecticides, effective against a wide range of flying, crawling, chewing, and sucking insects of the orders *Coleoptera, Diptera, Hemiptera (Homoptera* and *Heteroptera), Hymenoptera, Lepidoptera, Orthoptera,* and *Thysanoptera.* They are used as household insecticides, as grain protectants, and to control pests on edible products just prior to harvest (Metcalf 1989). They are used in a variety of locations including

Table 5-1. U.S. Producers of Pyrethrins and Pyrethroids

Pyrethroid	Producer	Production Site
Bifenthrin	FMC Corporation	Baltimore, Maryland
Cyfluthrin	Bayer Corporation	Kansas City, Missouri; Shawnee, Kansas
Cypermethrin	Astra Zeneca	Cold Creek, Alabama
	FMC Corporation	Baltimore, Maryland
Esfenvalerate	Du Pont	Axis, Alabama
Fluvalinate	BASF Corporation	Beaumont, Texas
Permethrin	Astra Zeneca	Cold Creek, Alabama
	FMC Corporation	Baltimore, Maryland
Pyrethrins (Pyrethrum)	McLaughlin Gormley King	Chaska, Minnesota
	SureCo Incorporated	Fort Valley, Georgia

Source: SRI 2000

Table 5-2. Facilities that Produce, Process, or Use Pyrethroids

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
Bifenthrin				
FL	1	100,000	999,999	8
IL	1	10,000	99,999	8
TX	1	10,000	99,999	2, 3, 8
Cyfluthrin				
MO	1	100,000	999,999	8
TX	1	10,000	99,999	8
Permethrin				
AL	1	100,000	999,999	1, 4
AR	1	10,000	99,999	8
FL	1	1,000,000	9,999,999	8
GA	1	100,000	999,999	8
IL	1	10,000	99,999	8
LA	1	1,000	9,999	8
MD	1	1,000,000	9,999,999	1, 4
NJ	1	1,000	9,999	8
TN	1	10,000	99,999	8
TX	2	10,000	99,999	2, 3, 8, 10
WI	1	10,000	99,999	8
Resmethrin				
TX	1	10,000	99,999	8
Tetramethrin				
WI	1	10,000	99,999	8

Source: TRI99 2001

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses

Table 5-3. Acid and Alcohol Feedstocks in the Pyrethroids Synthesis

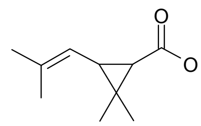
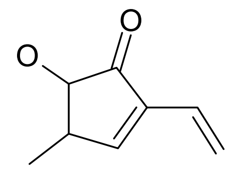
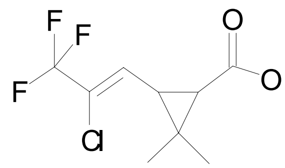
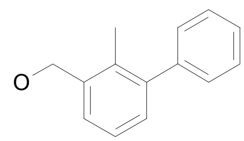
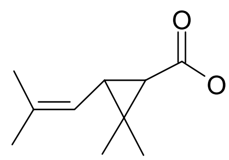
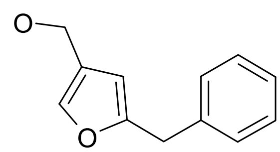
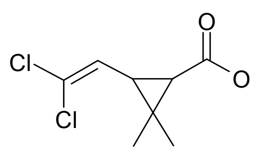
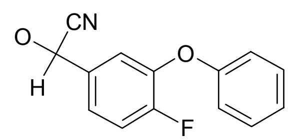
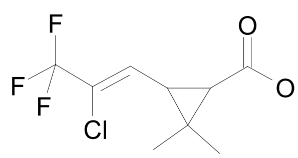
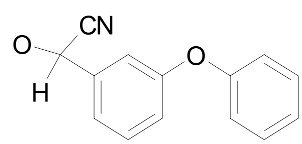
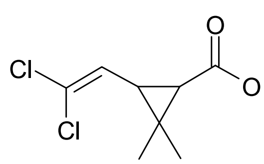
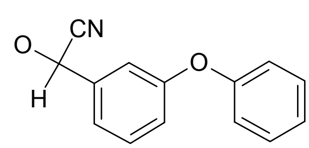
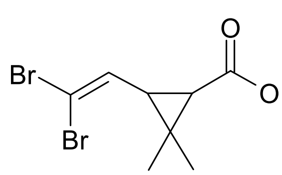
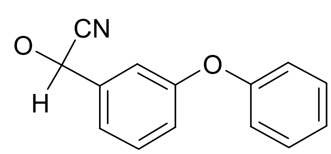
Pyrethroid	Acid	Alcohol
Allethrin		
Bifenthrin		
Bioresmethrin		
Cyfluthrin		
Cyhalothrin		
Cypermethrin		
Deltamethrin		

Table 5-3. Acid and Alcohol Feedstocks in the Pyrethroids Synthesis *(continued)*

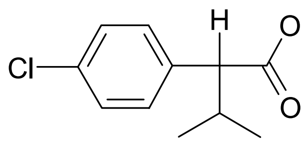
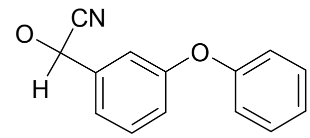
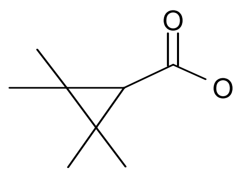
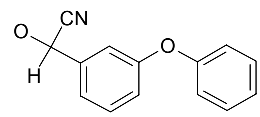
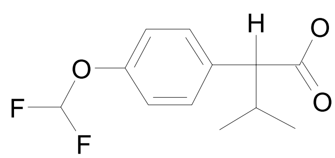
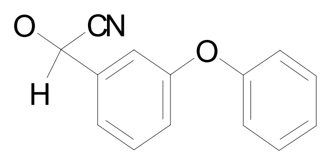
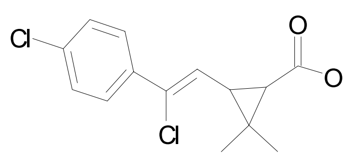
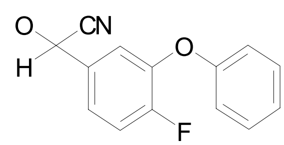
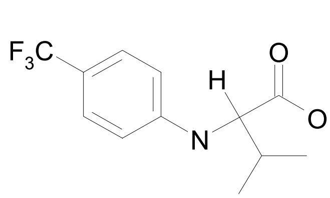
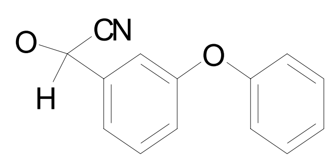
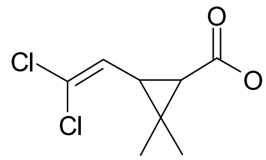
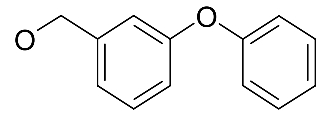
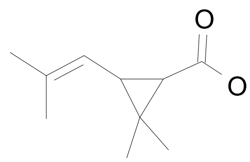
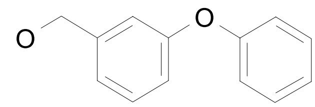
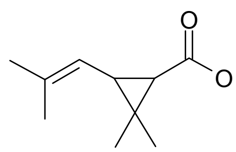
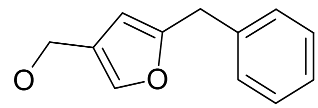
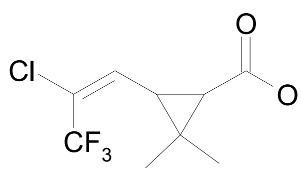
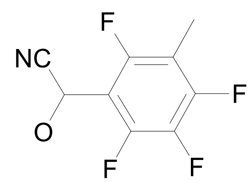
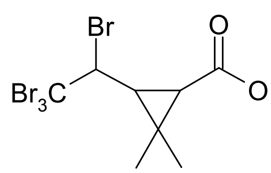
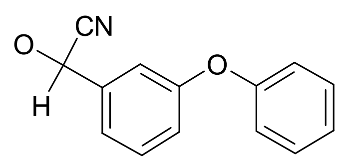
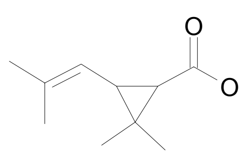
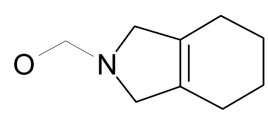
Pyrethroid	Acid	Alcohol
Esfenvalerate		
Fenproparthrin		
Flucythrinate		
Flumethrin		
Fluvalinate		

Table 5-3. Acid and Alcohol Feedstocks in the Pyrethroids Synthesis *(continued)*

Pyrethroid	Acid	Alcohol
Permethrin		
Phenothrin		
Resmethrin		
Tefluthrin		
Tralomethrin		
Tetramethrin		

Source: HSDB 2001

residential, public, and commercial buildings, animal houses, warehouses, fields, and green houses. They are also extensively used in the field of veterinary medicine (Davies 1985).

All concentrated formulations of pyrethroids were classified as restricted use pesticides by the EPA in 1995 (EPA 2000a). This classification restricts a pesticide to be used only by a certified applicator, or under the direct supervision of a certified applicator.

Detailed information regarding the amounts applied and use of individual pyrethroids is provided in Table 5-4. The data shown in Table 5-4 were developed from state-wide estimates of pesticide use rates on cropland and do not include pesticide applications to noncropland areas (i.e., home use, greenhouse use, etc.).

5.4 DISPOSAL

All pyrethrins and pyrethroids as well as piperonyl butoxide are listed as toxic substances under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1995). Disposal of wastes containing these compounds is controlled by a number of federal regulations (see Chapter 8). According to the TRI, in 1999, an estimated 1,239 pounds of permethrin were transferred off-site, presumably for disposal (TRI99 2001). No other pyrethroids or pyrethrins were reported as having off-site transfers in 1999 (TRI99 2001).

The EPA Office of Pesticide Programs has detailed labels for the use, storage, and disposal of all pesticides, including registered products containing pyrethrins and pyrethroids. All pesticide products are required to bear instructions for the storage and disposal of the pesticides and the pesticide containers. Storage and disposal instructions cover the appropriate storage of the pesticide product; disposal of any unused pesticide product or any rinse liquids resulting from cleaning of pesticide application equipment; and the disposal of the pesticide container. State and local regulations may be stricter than the federal requirements listed on the label.

Table 5-4. Uses of Pyrethroids

Pyrethroid	Amount[a] (pounds)	Insects[b,c,d]	Crops[b,c,d]	Other locations and applications[b,c]
Allethrin	NA	Flies, mosquitoes, ants	NA	Residential, public health, animal houses, topical application in pet sprays and shampoos
Bifenthrin	114,377	Beetles, weevils, houseflies, mosquitoes, lice, bedbugs, aphids, moths, cockroaches, locusts	Alfalfa hay, beans, cantaloupes, cereals, corn, cotton, field and grass seed, hops, melons, oilseed rape, potatoes, peas, raspberries, watermelons, squash	NA
Bioresmethrin	NA	Houseflies, mosquitoes, cockroaches	NA	Household, public health, animal houses
Cyfluthrin	151,422	Aphids, cabbage stem flea beetle, cockroaches house flies, mosquitoes, rape winter stem weevil	Alfalfa, cereals, cotton, citrus, deciduous fruit, ground nuts, maize, oilseed rape, pears, potatoes, rice, sugar beet, sugarcane, tobacco, vegetables	Green houses
Cyhalothrin	NA	Bedbugs, beetles, houseflies, ked, lice, mosquitoes, moths, weevils	NA	Public health, animal houses, inert surfaces
Cypermethrin	215,066	Cockroaches, flies, mosquitoes, moths	Cotton, lettuce, onions, pears, peaches, pecans, sugar beets	Residential and commercial buildings, animal houses
Deltamethrin	NA	Aphids, beetles, boll-worm, bud-worm, caterpillars, cicadas, codling moths, tortrix moths, weevils, whitefly, winter moths	Alfalfa, beet, cereals, coffee, cotton, figs, fruits, hops, maize, oilseed rape, olives, oil palms, potatoes, rice, soybeans, sunflowers, tea, tobacco, vegetables	Forests, households, animal houses, stored products
Esfenvalerate	215,919	Beetles, moths	Cabbage, corn, cotton, fruit trees, grains, groundnuts, maize, pecan, potatoes, sorghum, soybeans, sugar cane, sunflowers, sweet corn, tomatoes, vegetables, wheats	Ornamentals, non-crop land

Table 5-4. Uses of Pyrethroids *(continued)*

Pyrethroid	Amount[a] (pounds)	Insects[b,c,d]	Crops[b,c,d]	Other locations and applications[b,c]
Fenproparthrin	146,707	Aphids, armyworms, bollworms, bud-worms, cabbage looper, cabbage-worms, cutworms, diamondback moth, fruit moths, leaf-miners, leafrollers, leaf-worms, lepidopterous larvae, mites, mosquito, psyllas, stem-borers, ticks, tortrixies, tuber-worms, whiteflies	Cotton, citrus, fruits, pome, tomatoes, vegetables, vines	Glasshouse, ornamental trees
Flucythrinate	NA	Boll-worms, leaf-worms, sucking insects, whiteflies, beetles	Cotton, vines, strawberries, citrus fruit, bananas, pineapples, olives, coffee, cocoa, hops, vegetables, soybeans, cereals, maize, alfalfa, sugarbeet, sunflowers, tobacco	NA
Flumethrin	NA	Lice, ticks, psoroptic, chorioptic and sarcoptic munge	NA	NA
Fenvalerate	61,582	Beetles, cockroaches, flies, locusts, mosquitos, moths	Alfalfa hay, apples, beet, cereals, cotton, corn, cucurbita, fruit, green beans, groundnuts, hops, maize, nuts, oilseed rape, olives, potatoes, sorghum, soybeans, squash, sugarcane, sunflower, vegetables, vines, tobacco	Ornamentals, forestry, non-crop land
Fluvalinate	NA	Aphids, leaf-hoppers, moths, spider mites, thrips, white-flies	Apples, cereals, cotton, pears, peaches, tobacco, vegetables, vines	Outdoor and indoor ornamentals, turf
Permethrin	1,055,097	Ants, beetle, boll-worm, bud-worm, fleas, flies, lice, moths, mosquitos, termites, weevils	Alfalfa hay, corn, cotton, grains, lettuce, onion, peaches, potatoes, sweet corn, tomatoes, wheat	Home gardens, green houses, pet sprays, and shampoos
Phenotrhin	NA	Ants, bedbugs, cockroaches, fleas, houseflies, lice, mosquitoes, ticks	NA	Public buildings, stored grain, pet sprays, and shampoos

Table 5-4. Uses of Pyrethroids *(continued)*

Pyrethroid	Amount[a] (pounds)	Insects[b,c,d]	Crops[b,c,d]	Other locations and applications[b,c]
Resmethrin	NA	Flying and crawling insects, mosquitoes houseflies, german cockroaches	NA	Homes, greenhouses, indoor landscapes, mushroom houses, industrial sites
Tefluthrin	423,973	Beetles, houseflies, mosquitoes moths, weevils	Corn, maize, sugar beet, sweet corn	NA
Tetramethrin	NA	Flies, cockroaches, mosquitoes, wasps	NA	Public health, home and garden use
Tralomethrin	53,331	Aphids, beetles, cockroaches, moths, weevils	Cereals, coffee, cotton, fruit, maize, oilseed rape, rice, soybeans, tobacco, vegetables	Wood protection, homes, public health, stored grain, animal houses

[a]USGS 2001
[b]HSDB 2001
[c]Metcalf 1995
[d]Tomlin 1997

NA = not available

6. POTENTIAL FOR HUMAN EXPOSURE

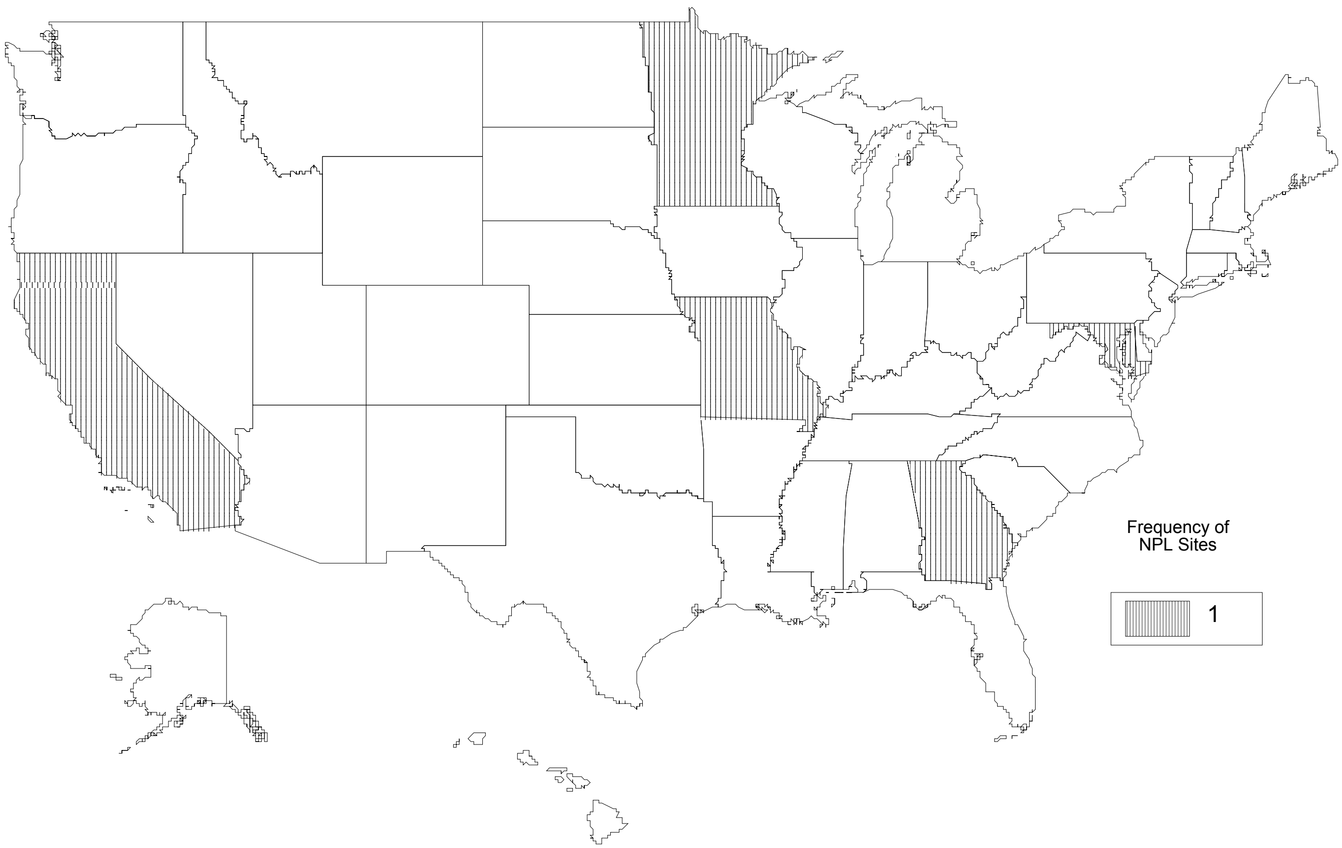
6.1 OVERVIEW

Pyrethrins have been identified in at least 5 of the 1,585 hazardous waste sites and permethrin has been found in at least 2 of the 1,585 current or former EPA National Priorities List (NPL) (HazDat 2001). However, the number of sites evaluated for these substances is not known. The frequency of these sites can be seen in Figures 6-1 and 6-2, respectively.

Pyrethrum is the natural extract derived from the flowers of *Chrysanthemum cinerariaefolium* and *Chrysanthemum cineum* (Metcalf 1995). Pyrethrum has long been recognized as possessing insecticidal properties, and the manufacture of flea and louse powders employing this extract began in Asia around 1800. The six active insecticidal compounds of pyrethrum are called pyrethrins. The individual pyrethrins are pyrethrin I, pyrethrin II, cinerin I, cinerin II, jasmolin I, and jasmolin II. These compounds are esters of two carboxylic acids (chrysanthemic acid and pyrethric acid) and three cyclopentenolones (pyrethrolone, cinerolone, and jasmolone). See Chapter 4 for the structures as well as the chemical and physical properties of these compounds. Synthetic pyrethroids are a diverse class of over 1,000 powerful insecticides that are structurally similar to the pyrethrins (Mueller-Beilschmidt 1990). Although they are based on the chemical structure and biological activity of the pyrethrins, the development of synthetic pyrethroids has involved extensive chemical modifications that make these compounds more toxic and less degradable in the environment. Products containing small amounts of pyrethroids for uses around the home are still classified as general use pesticides; however, emulsified or granular concentrate formulations that are applied to fields were classified as restricted use pesticides by the EPA in 1995 (EPA 2000a). The restricted use classification restricts a pesticide to be used only by a certified applicator, or under the direct supervision of a certified applicator. Although many pyrethroids have been developed, less than a dozen are used with any frequency in the United States, with permethrin being the most commonly employed pyrethroid.

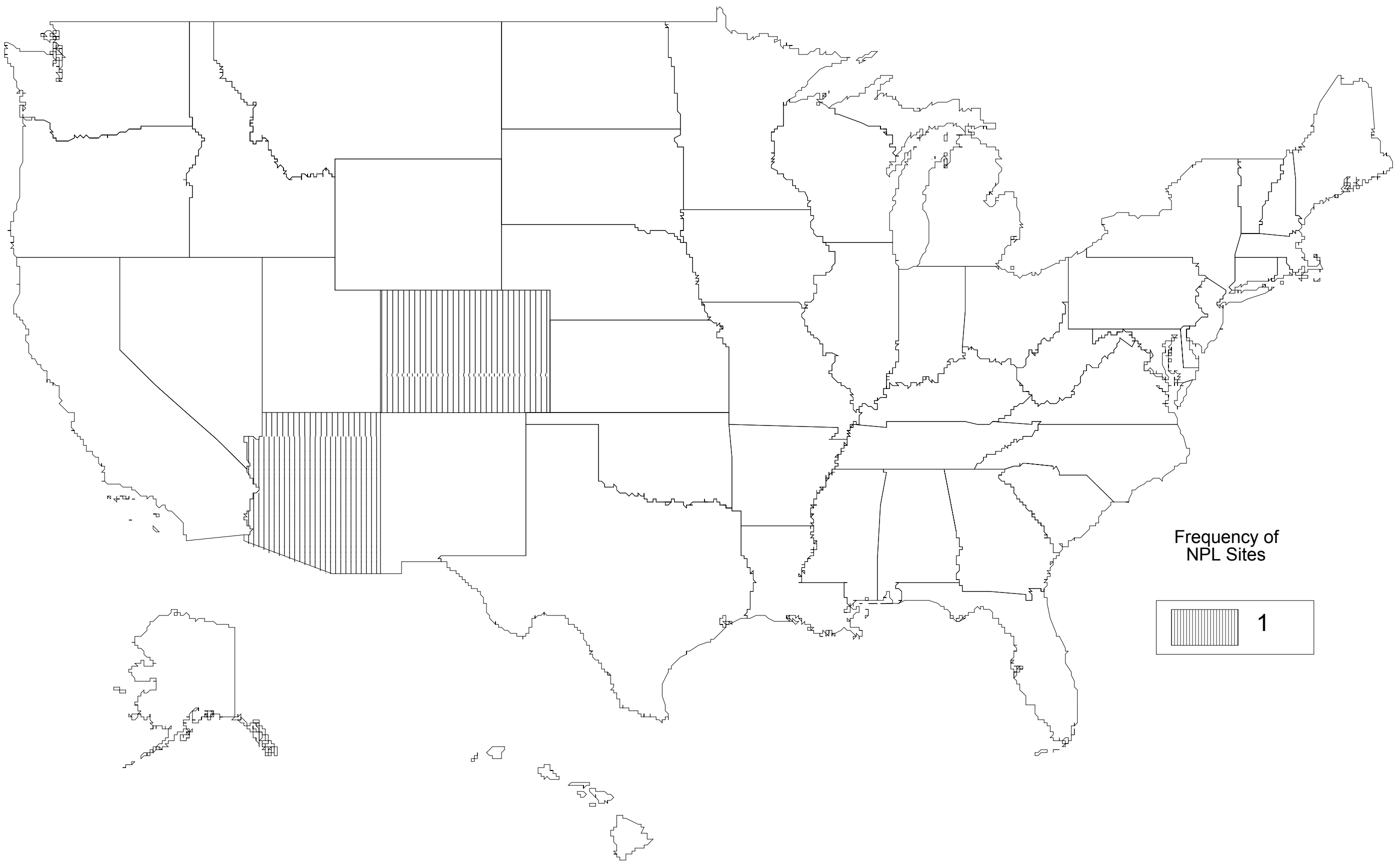
Pyrethrins and pyrethroids are released to the environment primarily as a result of their use as insecticides. These compounds are very important insecticides because of their rapid paralysis of flying insects, relatively low mammalian toxicity, and rapid rate of degradation in the environment. Often, pyrethrins and pyrethroids are formulated with compounds such as piperonyl butoxide, piperonyl sulfoxide, and sesamex, which act as synergists to increase the effectiveness of the insecticide.

Figure 6-1. Frequency of NPL Sites with Pyrethrins Contamination



Derived from HazDat 2001

Figure 6-2. Frequency of NPL Sites with Pyrethroid Contamination



Derived from HazDat 2001

Pyrethrins are rapidly detoxified by enzymes of insects and often, the paralyzed insect may survive and recover neurological function before mortality. The synergists are relatively nontoxic by themselves, but prevent the insect from detoxifying the active insecticide, thus increasing their effectiveness. At sufficient levels, the synergists may also increase the toxicity of pyrethrins and some pyrethroids in mammals. Pyrethrins are largely used indoors against flying insects in sprays, pet shampoos, and aerosol bombs, which contain about 0.04–0.25% of active ingredient and about 5–10 times this amount of piperonyl butoxide or other synergists to attenuate detoxification (Metcalf 1989). They also can be employed in multi-purpose insecticides for use on livestock, grains, fruits, and vegetables. Since the pyrethrins are not very stable when exposed to sunlight, their outdoor use on crops has diminished as relatively light stable pyrethroids have been developed. The different pyrethroids are used in many ways to control a wide variety of insects on crops, pets, and livestock. The toxicity of the pyrethroids are influenced by the isomeric properties of the compound. For pyrethroids possessing the cyclopropane moiety, the trans isomers tend to be rapidly eliminated by mammals and possess less toxicity than the cis isomers. For example, the oral LD_{50} (rats) of 1R cis resmethrin is about 168 mg/kg, but the value for the 1R trans isomer is >8,000 mg/kg (Dorman and Beasley 1991). Pyrethroids that contain the alpha-S-cyano phenoxybenzyl alcohol moiety demonstrate considerably greater toxicity when compared to the R configuration (Dorman and Beasley 1991). The enhanced insecticidal activity of esfenvalerate over fenvalerate is one example of this (Tomlin 1997). Esfenvalerate has become the preferred compound in the United States because it requires lower application rates than fenvalerate and is thus a more powerful insecticide. Esfenvalerate contains a much higher percentage of the alpha-S-cyano phenoxybenzyl alcohol isomer than fenvalerate. For most of the pyrethroids discussed, the approximate isomeric ratios of the technical grade products have been reported by Tomlin (1997).

The most important route of exposure to pyrethrins and pyrethroids for the general population is through the ingestion of foods, especially vegetables and fruits that have been sprayed with these insecticides. Farmers, pesticide applicators, and persons using these insecticides on a regular basis may also receive additional exposure through inhalation and dermal contact. Many of these compounds are employed in household products such as pet shampoos, household sprays, mosquito repellents, and lice treatments, and the general population can be exposed to these compounds through these uses.

The natural pyrethrins and many pyrethroids are rapidly degraded in the environment via photolysis, hydrolysis, and biodegradation. The environmental persistence times of many of these compounds are in the range of 1–2 days. The least persistent pyrethroids are allethrin, phenothrin, resmethrin, and tetramethrin. Structural modifications have made certain pyrethroids such as permethrin, cypermethrin, cyfluthrin, cyhalothrin, deltamethrin, fenvalerate, tefluthrin, and tralomethrin more persistent. For this reason, these compounds are utilized more often outdoors on crops than the relatively light unstable pyrethroids and pyrethrins. Pyrethrins and pyrethroids are extremely toxic to fish and environmentally beneficial insects such as bees. The natural pyrethrins and several pyrethroids are relatively nontoxic to mammals, but some pyrethroids such as deltamethrin, flucythrinate, cyhalothrin, permethrin, and tefluthrin have demonstrated considerable toxicity (Metcalf 1995). For example, flea applications containing a high concentration of permethrin made for use on dogs have often been associated with the accidental poisoning of cats when improperly used.

In soils, these compounds adsorb strongly and do not leach appreciably into groundwater. These compounds are not considerably taken up by the roots of vascular plants; however, they are deposited upon the leafy region of vegetation following spraying. In general, most of these compounds have relatively low vapor pressures and Henry's law constants, and as a result, volatilization from soil and water surfaces occurs slowly. Volatilization from foliage and household surfaces such as glass windows or floors occurs more rapidly since these compounds do not adhere to these surfaces as strongly in comparison to soils.

6.2 RELEASES TO THE ENVIRONMENT

Pyrethrum is found naturally in the environment as a constituent of *Chrysanthemum cinerariaefolium* and *Chrysanthemum cineum* (Metcalf 1995). However, the majority of releases of pyrethrins and pyrethroids are due to their use as insecticides. The estimated amounts of bifenthrin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, esfenvalerate, fenpropathrin, fenvalerate, permethrin, tefluthrin, and tralomethrin applied to crops in the United States in 1992 and 1997 are summarized in Table 6-1 (Gianessi and Silvers 2000). No data were identified for any other pyrethroid or any of the pyrethrins. Similar findings have been reported by the United States Geological Survey (USGS) 1992 Census of Agriculture (USGS 2001) (See Table 5-4).

Table 6-1. Trends of National Pyrethroid Use

Pyrethroid	Amounts applied (pounds) 1992	Amounts applied (pounds) 1997	Percent change
Bifenthrin	116,716	110,246	-5
Cyfluthrin	124,360	177,782	+43
lambda Cyhalothrin	205,329	321,284	+57
Cypermethrin	228,082	187,991	-18
Deltamethrin	0	27,045	
Esfenvalerate	331,522	228,885	-31
Fenpropathrin	66,368	31,839	-49
Fenvalerate	66,281	0	-100
Permethrin	1,068,598	1,066,056	-1
Tefluthrin	238,429	576,865	+142
Tralomethrin	60,105	23,767	-60

Source: Gianessi and Silvers 2000

6.2.1 Air

Releases to the air represent the most important emission pathway of pyrethrins and pyrethroids. Most applications of these insecticides involve aerial or ground spraying of crops or other vegetation, as well as the use of aerosol bombs and sprays indoors.

Manufacturing facilities may also release pyrethrins and pyrethroids during their production. A list of chemicals has been compiled for which releases are required to be reported to the EPA for the SARA Section 313 Toxics Release Inventory (TRI) (EPA 1995). The only pyrethroids that are on the list are allethrin, bifenthrin, cyfluthrin, cyhalothrin, fenpropathrin, fluvalinate, permethrin, phenothrin, resmethrin, and tetramethrin (TRI99 2001). Furthermore, data have only been reported for bifenthrin, cyfluthrin, permethrin, resmethrin, and tetramethrin. According to the TRI (Table 6-2), an estimated total of 546 pounds of bifenthrin, 16 pounds of cyfluthrin, 2,593 pounds of permethrin, 22 pounds of resmethrin, and 10,080 pounds of tetramethrin were discharged to air from manufacturing and processing facilities in the United States in 1999 (TRI99 2001). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

No pyrethrins or pyrethroids were identified in air samples from the 1,585 NPL hazardous waste sites (HazDat 2001).

6.2.2 Water

Direct releases to water are expected to be low for pyrethrins and pyrethroids because these compounds are primarily applied aerially or from ground-based sprayers directly to crops and vegetation. Spray drift following the application of these compounds, however, may contaminate nearby waters. Pyrethroids such as resmethrin, phenothrin, and permethrin, which are often used in mosquito control, are prohibited from being applied to open water or within 100 feet of lakes, rivers, and streams due to their high toxicity to fish (EPA 2000b).

Runoff water from fields or waste water from manufacturing facilities may contain pyrethrins and pyrethroids. For example, pyrethrin I and II were detected in runoff water following the application of a multi-purpose insecticide containing pyrethrins to a field in Franklin County, Kentucky (Antonious et al. 1997). Leachate collected near a pesticide manufacturing plant in Barcelona, Spain contained

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Pyrethroids

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on- and off-site release
Bifenthrin								
FL	1	36	0	No data	No data	36	No data	36
IL	1	10	No data	No data	No data	10	No data	10
MD	1	No data	No data	No data	No data	No data	No data	No data
NY	1	No data	No data	No data	No data	No data	No data	No data
TX	1	500	No data	No data	No data	500	No data	500
Total	5	546	0	0	0	546	0	546
Cyfluthrin								
MD	1	No data	No data	No data	No data	No data	No data	No data
MO	1	11	72	No data	No data	83	No data	83
NJ	1	No data	No data	No data	No data	No data	No data	No data
TX	2	5	No data	No data	No data	5	No data	5
Total	5	16	72	0	0	88	0	88
Permethrin								
AL	1	497	0	No data	No data	497	4	501
AR	2	500	No data	No data	No data	500	1,235	1,735
AZ	1	No data	No data	No data	No data	No data	No data	No data
FL	1	193	0	No data	No data	193	No data	193
GA	2	1	No data	No data	No data	1	No data	1
IL	2	10	No data	No data	No data	10	No data	10
LA	2	10	No data	No data	31,000	31,010	No data	31,010
MD	1	10	0	No data	No data	10	No data	10
MN	1	No data	No data	No data	No data	No data	No data	No data
MO	2	No data	No data	No data	No data	No data	No data	No data

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Pyrethroids (*continued*)

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on- and off-site release
NJ	1	No data	No data	No data	No data	No data	No data	No data
TN	1	751	No data	No data	No data	751	No data	751
TX	4	621	No data	No data	No data	621	No data	621
WI	1	0	No data	No data	No data	0	No data	0
Total	22	2,593	0	0	31,000	33,593	1,239	34,832
Resmethrin								
GA	1	No data	No data	No data	No data	No data	No data	No data
MO	1	No data	No data	No data	No data	No data	No data	No data
TX	1	22	No data	No data	No data	22	No data	22
Total	3	22	0	0	0	22	0	22
Tetramethrin								
IN	1	10,080	No data	No data	No data	10,080	No data	10,080
MN	1	No data	No data	No data	No data	No data	No data	No data
MO	1	No data	No data	No data	No data	No data	No data	No data
WI	1	0	No data	No data	No data	0	No data	0
Total	4	10,080	0	0	0	10,080	0	10,080
Grand Total	39	13,257	72	0	31,000	44,329	1,239	45,568

Source: TRI99 2001

[a]Data in TRI are maximum amounts released by each facility.
[b]Post office state abbreviations are used.
[c]The sum of fugitive and stack releases are included in releases to air by a given facility.
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[e]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

cypermethrin at concentrations exceeding 5–10 ppm (Rivera et al. 1985). Fenvalerate was detected in runoff water from an agricultural region in the Nicolet River Basin of Quebec, Canada at an average concentration of 0.05 µg/L in June of 1989 (Caux et al. 1996).

According to the TRI, an estimated total of 72 pounds of cyfluthrin (Table 6-2) was discharged to water from manufacturing and processing facilities in the United States in 1999 (TRI99 2001). The data listed in the TRI should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

No pyrethrins or pyrethroids were identified in groundwater or surface water samples of the 1,585 NPL hazardous waste sites (HazDat 2001).

6.2.3 Soil

Releases of pyrethrins and pyrethroids to soils typically result from deposition following aerial or boom spraying of crops or vegetation. Improper disposal also may account for some sources in soil.

According to the TRI, 31,000 pounds of permethrin were discharged to land from manufacturing and processing facilities in the United States in 1999 (TRI99 2001). The data listed in the TRI should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Pyrethrins were identified in soil samples collected at 2 of the NPL hazardous waste sites where it was detected in some environmental media (HazDat 2001). No pyrethroids were identified in soil samples of the 1,585 NPL hazardous waste sites.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Spray drift following the application of any pesticide is an important source of environmental contamination and is responsible for much of the aerial transport of these compounds. Spray drift is simply the movement of the applied insecticide outside the intended target area by mass transport or diffusion. The characteristics of spray drift are influenced largely by meteorologic conditions and the method of application. Wind velocity is the dominant environmental factor that affects spray drift. Droplet size, height of flight, aircraft speed, and boom length are the dominant spraying and equipment factors that affect spray drift. Application parameters can be optimized, but they are different for different insecticides (e.g., some insecticides are more effective with large droplets and/or high spray rates and others are more effective with small droplets and/or low spray rates). In an aerial deposition study of deltamethrin involving spray application from an airplane, peak deposition to the ground was 0.5–1.2 ng/cm^2 (Johnstone et al. 1987). A site 4 km away from the spray zone received ground depositions as high as 0.2 ng/cm^2, although most areas outside the spray zone received insignificant deposition. During application of insecticides to an apple orchard in Massachusetts approximately 1 acre in size, fenvalerate was detected downwind of the spray zone (75 feet away) at a maximum concentration of 1.28 μg/m^3 (Clark et al. 1991). Within 2 hours, the level had been reduced to 0.03 μg/m^3.

Based on the vapor pressure of the pyrethrins and pyrethroids (Tables 4-4 and Table 4-5, respectively), these compounds are expected to exist in both the vapor and particulate phases in the ambient atmosphere. Vapor phase pyrethrins and pyrethroids are rapidly degraded in the atmosphere by direct photolysis and reaction with oxidants found in air such as photochemically-produced hydroxyl radicals, ozone, and nitrate radicals. Particulate phase compounds are slower to degrade, however, and can travel long distances before being removed from the air by wet and dry deposition. The concentrations of 13 different pesticides in the atmosphere and rainfall was studied in an area of eastern France in 1992 (Millet et al. 1997). Fenpropathrin was detected in the vapor phase at concentrations ranging from 0.03–2.7 ng/mL and in the particulate-phase at concentrations of 0.03–4 ng/mL (Millet et al. 1997).

Pyrethrins and pyrethroids are strongly adsorbed to soil surfaces and are not considered very mobile. A wide range of K_{oc} values have been reported by different authors, but most of these values indicate a high degree of adsorption and little leaching potential. The K_{oc} values for the pyrethrins were estimated to range from 700 (cinerin II) to 27,200 (pyrethrin I) (Crosby 1995). Adsorption data are available for several pyrethroids from the U.S. Department of Agriculture Pesticide Database (USDA 2001a). The K_{oc} values for permethrin range from 10,471 to 86,000. The K_{oc} values in a silt loam, sandy loam, sediment, and sand were 19,340, 20,865, 44,070, and 60,870, respectively. The K_{oc} values of cypermethrin in loamy sand (pH 5.4, 2.1% organic matter), sandy loam (pH 6.5, 3.4% organic matter), silt loam (pH 5.6, 2.0% organic matter), loamy sand (pH 4.7, 15.6% organic matter), and loam (pH 7.1, 5.2% organic matter) were 160,000, 84,000, 22,000, 34,000, and 5,800, respectively (USDA 2001a). The K_{oc} values for cyfluthrin range from 3,700 to 64,125, the values for fenvalerate range from 1,000 to 12,000, and the values for fenpropathrin range from 5,000 to 340,000. The movement of deltamethrin, cypermethrin, permethrin, and their degradation products were studied in clay and loamy sands (Kaufman et al. 1981). Deltamethrin, permethrin (both cis and trans isomers) and cypermethrin (both cis and trans isomers), were considered immobile in all soils tested. The degradation products studied, cis, trans 3-(2,3-dichloro-ethenyl)-2,2-dimethylcyclopropanecarboxylate, 3-phenoxybenzyl alcohol, and 3-phenoxybenzoic acid showed some level of mobility.

Volatilization from water and soil is expected to occur slowly for many of the pyrethroids since these compounds generally have low vapor pressures and Henry's law constants (Table 4-5). When released to water, partitioning to suspended solids and sediment occurs rapidly. These compounds adsorb strongly to suspended solids and sediment in the water column, and this process significantly attenuates volatilization. Laboratory studies indicated that over 95% of an initially applied amount of permethrin was adsorbed onto lake sediment and only 7–9% of the adsorbed complex could be desorbed from the sediment following 4 successive rinses with distilled water (Sharom and Solomon 1981). Compounds with relatively large Henry's law constants, such as deltamethrin, volatilize more readily from water surfaces than other pyrethroids. Muir et al. (1985) determined that after deltamethrin was applied to ponds, approximately 6% volatilized over the course of a 2-day incubation period. However, the major partitioning process was adsorption to suspended solids and sediment. Maguire et al. (1989) observed that deltamethrin applied to a pond in Canada was rapidly dissipated by photolysis, hydrolysis, and volatilization. Laboratory studies using sterilized pond water showed that volatilization losses increased if the deltamethrin was sprayed directly onto the surface of the water rather than injecting the solution into the subsurface water. Volatilization losses from foliage may be considerably greater than volatilization from soils because pyrethrins and pyrethroids do not adsorb as strongly to the leafy component of vegetation as to soils (Boehncke et al. 1990). Laboratory and field tests were conducted to evaluate volatilization losses of deltamethrin sprayed on plant and soil surfaces (Boehncke et al. 1990). Under the summer time conditions of the field tests, mean evaporative losses from lettuce, kohlrabi, green beans, and summer wheat ranged from 12–71% over a 24-hour period, while evaporative losses from soil were approximately 24% in 24 hours. Since pyrethrin I, cinerin I, and jasmolin I have larger Henry's law constants than the corresponding esters (pyrethrin II, cinerin II, and jasmolin II), they are expected to volatilize from moist soils and water more rapidly. The estimated volatilization half-lives of pyrethrin I, cinerin I, and jasmolin I from soil range from 1.8–2.7 days, while the half-life values for pyrethrin II, cinerin II, and jasmolin II range from 36.8–97 days (Crosby 1995). Pyrethrins and pyrethroids are often used indoors in sprays or aerosol bombs, and the volatilization rates from glass or floor surfaces may be significantly faster than from soils since these compounds are not likely to adsorb as strongly to these surfaces.

Pyrethrins and pyrethroids can bioconcentrate in aquatic organisms and are extremely toxic to fish. The bioconcentration factor (BCF) of permethrin, fenvalerate, deltamethrin, and cypermethrin in rainbow trout (*Oncorhynchus mykiss*) and sheepshead minnow (*Cyprinodon vagiegatus*) were approximately 450–600, 180–600, 100–1,200 and 120–400, respectively (Haitzer et al. 1998). The BCF values varied considerably as the amount of dissolved organic matter in the water column was changed (Haitzer et al. 1998). The steady-state BCF values of fenvalerate and permethrin in eastern oysters (*Crassostrea virginica)* were measured as 4,700 and 1,900, respectively over a 28-day incubation period (Schimmel et al. 1983). In pesticide-free water, the contaminated oysters depurated permethrin and fenvalerate to nondetectable levels in 1 week. Insect BCF values after 6 hours of exposure to sublethal permethrin concentrations were 18, 30, 7, 4, and 24 for black fly, caddisfly, damsefly, water scavenger, and mayfly, respectively (Tang and Siegfried 1996). Using a static test system and a 3-day incubation period, the BCF value for cypermethrin in golden ide fish (*Leuciscus idus melanotus*) was measured as 420 (Freitag et al. 1985). In a series of field tests designed to simulate the environmental fate of tralomethrin and deltamethrin due to spray drift and field runoff, fathead minnows were exposed to different levels of these pyrethroids (Erstfeld 1999). Over the course of a 7-day incubation period, the minnows were analyzed and BCF values of 219 and 315 were calculated for days 4 and 7, respectively, for the tralomethrin spray drift pond microcosms. The BCF values were 185 and 143 for days 4 and 7, respectively, for the tralomethrin runoff water microcosms. The BCF values were 260 and 185 for days 4 and 7, respectively, for the deltamethrin spray drift pond microcosms and the BCF values were 169 and 166 for days 4 and 7, respectively, for the deltamethrin runoff water microcosms.

Little data exist regarding the uptake and transport of pyrethrins and pyrethroids by plant material. Since many of these compounds are rapidly degraded in the environment, this transport mechanism may not be an important environmental fate process other than the initial settling of these compounds on the canopy following deposition. The aerial surface of a plant, including foliage, is covered by a cuticle, which serves as a barrier to water loss and to prevent penetration of applied chemicals or environmental pollutants (Paterson et al. 1990). Once deposited on the surface, a chemical may be degraded, bind to the cuticle, or diffuse into the plant through the stomata. Parihar and Gupta (1998) demonstrated that fenvalerate applied to the surface of pigeon pea (*Cajanus cajan*) in India under field conditions was rapidly degraded and did not accumulate significantly in the plants. The fenvalerate residues were below detection limits at 15 and 20 days postapplication for two different application rates. These compounds can also be taken up from the soil by the roots of the plant. Since pyrethrins and pyrethroids adsorb strongly to soils, their uptake from roots and transport within plants is expected to be limited. Lettuce, beets, and wheat planted in soil 30, 120, and 365 days after treatment of [^{14}C]-fenvalerate were shown to accumulate very little ^{14}C when harvested at maturity (Lee 1985). Furthermore, it was demonstrated that very little downward movement of the radiolabeled fenvalerate occurred in the soils and that little, if any, fenvalerate or its degradation products are taken up by the roots of these plants. Chemicals may enter aquatic plants in solution directly from the water. Erstfeld (1999) demonstrated that aquatic plants accumulate deltamethrin and tralomethrin from the water column, in a series of pond and runoff water microcosms. Following application of tralomethrin, the BCF values in macrophytes were 18,200 and 8,290 in pond and water runoff microcosms, respectively, at 7 days postapplication (Erstfeld 1999). This observation is consistent with the data of Muir et al. (1985) that observed deltamethrin residues in aquatic plants at concentrations ranging from 253–1,021 ng/g 24 hours after application of 1.8–2.5 µg/L deltamethrin solution to a pond. Similarly, permethrin applied to the surface of a fast-flowing stream was taken up by aquatic plants (Sundaram 1991). Following application of 1.658 g of permethrin to the stream surface, permethrin concentrations in aquatic plants located 280 m from the application site ranged from 6.78 ng/g (420 minutes postapplication) to 17.6 ng/g (60 minutes postapplication). It was concluded that the permethrin was largely absorbed in foliar waxes in the water arum and was slowly desorbed and lost by hydrolytic or microbial degradation.

6.3.2 Transformation and Degradation

Many studies use first-order kinetics to model the dissipation of pesticides in the environment because a half-life for the chemical can be defined. The half-life represents the calculated time for loss of the first 50% of the substance. However, in many cases, the time required for the loss of the remaining substance may be substantially longer, and the rate of disappearance may decline further as time progresses. This is often the case for the disappearance of pesticides in soils. For simplicity, the term half-life in this document is used to indicate the estimated time for the initial disappearance of 50% of the compound and does not necessarily imply that first-order kinetics were observed throughout the experiment unless otherwise noted.

6.3.2.1 Air

Pyrethrins and pyrethroids in the ambient atmosphere are degraded rapidly through reaction with atmospheric oxidants or by direct photolysis. Based upon rate constants for the reaction with hydroxyl radicals and ozone molecules derived from a structure estimation method (Meylan and Howard 1993), the atmospheric half-lives of the pyrethrins are on the order of several minutes to a few hours (HSDB 2001). These compounds are also rapidly degraded by direct photolysis. Chen and Casida (1969) observed that thin films of pyrethrin I applied to glass plates underwent 90% photodecomposition within 0.2 hours, while a dark control underwent very little loss.

Pyrethroids where the isobutenyl group attached to the cyclopropane moiety has been altered, are more stable to sunlight than the early pyrethroids like allethrin or resmethrin. For this reason, pyrethroids such as permethrin, deltamethrin, cyhalothrin, cyfluthrin, and cypermethrin are more frequently applied outdoors to crops in comparison to the rapidly degraded pyrethroids like resmethrin and allethrin. When exposed to daylight as a thin film indoors near a window, phenothrin decomposed with a half-life of about 6 days, whereas about 60% of applied permethrin remained undecomposed after 20 days (WHO 1990c [permethrin]). Thus, the replacement of the isobutenyl group with the dichlorovinyl substituent significantly enhanced the photostability of permethrin in comparison to phenothrin (WHO 1990c [permethrin]). The photodegradation half-life of permethrin on thin films exposed to light at 295–305 nm was in the range of 5–7 days, while the half-lives for deltamethrin and cis cypermethrin were 6 and 7.5 days, respectively (Chen et al. 1984). Cypermethrin exposed to ultraviolet (UV) light >290 nm, underwent 30.2% photomineralization over a 17-hour irradiation period (Freitag et al. 1985). The photodegradation half-life of tetramethrin on glass films exposed to a sunlamp was approximately 1 hour, with nearly 100% photodecomposition observed after 15 hours of illumination (Chen and Casida 1969). Allethrin applied to glass films was degraded approximately 90% in 8 hours when irradiated with UV light, but some of the loss was attributed to volatilization (Chen and Casida 1969). Aqueous suspensions of allethrin underwent approximately 11.1% photodecomposition after only 15 minutes of exposure to sunlight (Ivie and Casida 1971b). It was also observed that the addition of chloroplasts to the suspensions photosensitized the photolysis and increased degradation rates in sunlight, suggesting that photodegradation on crops is a very rapid process. The photolysis half-life of resmethrin films on glass plates ranged from about 20 to 90 minutes when exposed to forenoon and midday sunlight conditions (Samsonov and Makarov 1996). The fastest rates were observed during midday sunlight and in the presence of the sensitizer methylene blue. Resmethrin also underwent direct photolysis when aerosols were irradiated with sunlight. Photodecomposition products of resmethrin included chrysanthemic acid, phenylacetic acid, benzyl alcohol, benzaldehyde, benzoic acid, and various chrysanthemates (Ueda et al. 1974). Cyhalothrin was reported as being stable to light, with <10% photodecomposition after 20 months while stored under sunlight conditions (Tomlin 1997). However, on soil surfaces and in aqueous solutions at pH 5, cyhalothrin was degraded upon exposure to sunlight with a reported half-life of about 30 days (WHO 1990a [cyhalothrin]).

Compounds, such as nitroanilines, that absorb light in the environmental UV spectrum have been shown to photostabilize pyrethrins and pyrethroids (Dureja et al. 1984). Following irradiation at 360 nm for 18 hours the percent recoveries of pyrethrins, allethrin, kadethrin, resmethrin, tetramethrin, phenothrin, and fenpropathrin on silica gel plates were 1, 2, 0, 7, 2, 29, and 28%, respectively (Dureja et al. 1984). Following the addition of the herbicide trifluralin, the amounts recovered after irradiation were: pyrethrins, 54%; allethrin, 78%; kadethrin, 47%; resmethrin, 85%; tetramethrin, 77%; phenothrin, 66%; and fenpropathrin, 83% (Dureja et al. 1984). Pyrethroids with halogenated acid moieties were also protected from photodecomposition due to the addition of trifluralin. Following irradiation at 360 nm for 32 hours on silica gel plates, the percent recoveries of permethrin, cypermethrin, deltamethrin, and fenvalerate were 32, 19, 25, and 23%, respectively. With the addition of trifluralin, the percent recoveries increased to 65% for permethrin, 83% for cypermethrin, 57% for deltamethrin, and 90% for fenvalerate (Dureja et al. 1984). Deltamethrin impregnated cotton strips were degraded upon irradiation with UV light at differing rates, depending upon the color of the fabric and whether or not a UV absorber was added to the impregnating solution (Hussain and Perschke 1991). When white cotton fabric treated with deltamethrin alone was irradiated for 24 hours, nearly 100% photodegradation was observed. However, deltamethrin applied to blue and black fabric was degraded approximately 44.9 and 37.5%, respectively, over a 24-hour irradiation period (Hussain and Perschke 1991). Addition of the UV absorber 2,4-dihydroxybenzophenone also decreased the amount of degradation following exposure to UV light.

6.3.2.2 Water

Since pyrethrins and pyrethroids undergo photolysis in the atmosphere, they are also degraded by this mechanism in sunlit surface waters. Photosensitizing agents found in natural waters such as fulvic and humic acids increase the rate of photolysis. The photolysis half-life of permethrin in seawater exposed to outdoor light was determined to be 14 days and the half-life of fenvalerate was measured as 8 days

(Schimmel et al. 1983). Little change in concentration was observed when each pyrethroid was incubated in dark constant temperature controls. Photolysis half-lives of 27.1 and 19.6 hours were determined for respective cis and trans isomers of permethrin in 800 mL of pond water exposed to sunlight (Rawn et al. 1982). The photodegradation half-life of cypermethrin in a distilled water solution ranged from 2.6–3.6 days and the half-lives in river and seawater were in the range of 0.6–1.0 days when exposed to sunlight (Takahashi et al. 1985a). The cis isomers underwent photodegradation at slightly greater rates than the trans isomers. The photodegradation half-life of deltamethrin in distilled water was 1–2 days, while the half-life in river water was slightly longer, yet still <5 days when solutions were exposed to sunlight (Maguire 1990). The photolysis half-lives of fenpropathrin in distilled water, distilled water with humic acid, river water, and seawater were 13.5, 6, 2.7, and 1.6 weeks, respectively when exposed to sunlight (Takahashi et al. 1985c).

These compounds also undergo hydrolysis in the environment at varying rates depending upon pH and temperature. Generally, hydrolysis is only an important environmental fate process under alkaline conditions and at temperatures of 20 EC or greater. The hydrolysis half-life of cyfluthrin is about 231 days at pH 7, but about 2 days at pH 8 (USDA 2001a). At pH 5 and pH 7, permethrin is stable towards abiotic hydrolysis, but at pH 9, the abiotic hydrolysis half-life is about 50 days (USDA 2001a). The aqueous hydrolysis half-lives of cypermethrin in sterile water-ethanol (99:1) phosphate buffers at 25 EC were determined to be 99, 69, 63, and 50 weeks at pH values of 4.5, 6, 7, and 8, respectively (Chapman and Cole 1982). The half-lives of an 8 ppb solution of fluvalinate at 25 EC were 48, 22.5, and 1.13 days at pH 5, 7, and 9, respectively (Tomlin 1997). The hydrolysis of fenpropathrin in buffer solution was studied under various pH and temperature conditions (Takahashi et al. 1985b). At 25 EC, the hydrolysis half-lives of fenpropathrin were approximately 2.2 years and 8 days at pH 7 and 9, respectively (Takahashi et al. 1985b). At 40 EC, the half-lives were about 80 days and 19 hours at pH 7 and 9, respectively (Takahashi et al. 1985b).

Pyrethroids are readily degraded by environmental microorganisms. The half-life of permethrin in a sediment/seawater solution was <2.5 days, but under sterile conditions, there was no significant change in the permethrin concentration over a 4-week incubation period, suggesting that biodegradation was responsible for the loss under nonsterile conditions (Schimmel et al. 1983). The half-life of fenvalerate in the sediment/seawater solution was 27–42 days under nonsterile conditions and little loss was noted under sterilized conditions (Schimmel et al. 1983). A series of pond and runoff water microcosms were constructed to simulate the fate and persistence of tralomethrin and deltamethrin under field conditions following spray drift over a 7-day study period (Erstfeld 1999). The degradation profiles of tralomethrin in water showed rapid conversion to deltamethrin with a calculated half-life of about 6.8 hours. The resulting deltamethrin was further degraded to decamethrinic acid with a half-life of about 81 hours. In sediment, tralomethrin was rapidly converted to deltamethrin. Two experiments were conducted to evaluate the persistence of fenvalerate in seawater and seawater/sediment microcosms under different conditions (Cotham and Bidleman 1989). The half-lives of fenvalerate in unsterilized seawater at pH 8 and 8.05 were 17 and 14 days, respectively. The half-lives of fenvalerate in heat sterilized seawater at pH 8 and 8.05 were 41 and 33 days, respectively (Cotham and Bidleman 1989). Bioresmethrin, cypermethrin, deltamethrin, permethrin, fenvalerate, and Nuerelle DX 50 (50 grams cypermethrin and 500 grams chlorpyriphos mixture) were degraded at different rates in a model ecosystem consisting of polluted river water and sediment under aerobic conditions (Lutnicka et al. 1999). The temperature of the ecosystem was 15–19 EC and the pH was 7.7. The ranges of half-lives in the model ecosystem were: bioresmethrin, 1.2–4.6 days; cypermethrin, 4.7–30.8 days; deltamethrin, 0.5–0.8 days; permethrin, 1.1–3.6 days; fenvalerate, 3.5–4.4 days; and cypermethrin in the Nuerelle DX 50 mixture, 11.6–30.4 days (Lutnicka et al. 1999). It was also noted that the degradation rates of the pyrethroids followed first-order kinetics, and that only fenvalerate and cypermethrin residues remained at detectable levels 56 days postapplication.

No data exist regarding the degradation of pyrethrins in water. Based upon degradation studies of structurally similar esters and the degradation rates of the pyrethroids, it has been concluded that pyrethrins should degrade rapidly in water (Crosby 1995).

6.3.2.3 Soil

Laboratory and field studies suggest that pyrethroids are degraded faster in soils than many of the long lasting organochlorine, organophosphorus and carbamate pesticides. Fenvalerate and deltamethrin appear to be the most persistent compounds in commercial use, especially in soils containing a high clay content or a large percentage of organic matter.

Chapman et al. (1981) studied the persistence of permethrin, cypermethrin, deltamethrin, fenpropathrin, and fenvalerate in sterile and nonsterile soils in order to assess the importance of biodegradation versus abiotic transformation mechanisms. After initial application of 1 ppm of each pyrethroid in a mineral soil, the percentages of pesticide recovered after an 8-week incubation period were: fenpropathrin, 2%;

permethrin, 6%; cypermethrin, 4%; fenvalerate, 12%; and deltamethrin, 52%. Over 90% of each pyrethroid was recovered from heat sterilized soils, suggesting that biodegradation plays a crucial role in the disappearance of these compounds. Similar results were obtained in a richly organic soil, although the amounts degraded were slightly lower over the 8-week incubation period. In the organic soil, the percent recoveries after 8 weeks were as follows: fenpropathrin, 8%; permethrin, 16%; cypermethrin, 16%; fenvalerate, 58%; and deltamethrin, 74%. The USDA Pesticide Database lists half-lives in the range of 88–287 days for fenvalerate, 56–63 days for cyfluthrin, 4–40 days for permethrin, and 6–60 days for cypermethrin in aerobic soils (USDA 2001a). In a biodegradation study using deltamethrin as the sole carbon source and pure bacterial isolates from soil as inoculum, 35.7–44.4% of the initially applied deltamethrin metabolized in 1 week and 59.7–72.5% was degraded in 2 weeks (Khan et al. 1988). In the absence of bacterial isolates, only 3–10% of the deltamethrin was degraded. Deltamethrin was applied to a sandy loam from Alberta, Canada at an initial fortification level of 17.5 g/ha (42.5 ppb) and studied under indoor laboratory conditions and field conditions over a 52-week incubation period (Hill 1983). The half-life of deltamethrin under the field conditions was 6.8 weeks and approximately 5–7% of the applied deltamethrin remained after 52 weeks. The half-life of the deltamethrin in the indoor experiments was 4.8 weeks and the difference in persistence between the field and laboratory experiments were attributed to climate effects. In both cases, the degradation was exponential and the decay could be reasonably fit to first-order kinetic equations (Hill 1983). It was noted that in the field experiments, the rate of degradation was slowed during the winter months. The anaerobic degradation of cyfluthrin in heavy clay soils was studied under laboratory conditions for a period of 140 days at different moisture levels and organic matter content (Smith et al. 1995). The percentages of cyfluthrin recovered in an unamended soil after 31, 73, 115, and 140 days was 50.8, 27.9, 14.8, and 15%, respectively. The percentages of cyfluthrin recovered in a soil amended with organic matter from cotton plant residue were 35.2, 20.9, 14.4, and 9.4%, respectively, over the same incubation periods. The disappearance of cyfluthrin was not significantly affected by the moisture content of the soils (Smith et al. 1995). The half-lives of fluvalinate and flucythrinate in agricultural soil were 6.8–8.0 days and 9.4–11.9 days, respectively, depending upon the application rate (Agnihotri and Jain 1987). It was observed that the rate of disappearance followed first-order kinetics, and that after 40 days, neither insecticide remained at detectable levels in the soil (Agnihotri and Jain 1987). The half-life of fenvalerate in a tidal marsh sediment ecosystem, with sediment obtained from the Chesapeake Bay, was calculated as 6.3 days (0.2 ppm initial concentration) and 8.8 days (1 ppm initial concentration) (Caplan et al. 1984). It was not possible to determine the exact mechanism of degradation (hydrolysis, biodegradation or photolysis) since no dark or sterile controls were run; however biodegradation and hydrolysis were the most likely routes since the fenvalerate was initially incorporated into the sediment shielding it from substantial sunlight. The half-life of fenvalerate in a sediment/seawater (obtained from Charleston, South Carolina) system at pH 7.3–7.7 was 12 days (Cotham and Bidleman 1989). The half-lives of fenvalerate applied to sandy loam and silty clay loam soils at an initial concentration of 5 ppm were approximately 75–80 days under indoor laboratory conditions (Lee 1985). The half-life under outdoor conditions was approximately 60 days (Lee 1985).

Since light is attenuated as a function of depth from the soil surface, photolysis of pyrethrins and pyrethroids is only an important environmental fate process at the surface of the soil. The photodegradation of cypermethrin was studied by exposing various soil surface applications to sunlight for 7–10 days (Takahashi et al. 1985a). The half-lives on soil surfaces exposed to sunlight ranged from 0.6 to 1.9 days, while half-lives on non-illuminated soils were >7 days. The photodegradation products resulting from exposure of cypermethrin to sunlight included various carbanoyl and hydroxy derivatives, a variety of benzoic acid derivatives, several lactone derivatives, and several aliphatic carboxylic acid derivatives (Takahashi et al. 1985a). The photodegradation of esfenvalerate on thin films of soil, clay, and humic material was studied (Katagi 1991). Half-lives ranged from about 8 to 100 days with reaction at the cyano group and ether cleavage in the alcohol moiety responsible for the photodegradation on the surfaces tested. The shortest photolysis half-lives were observed when esfenvalerate was incorporated into the clay thin films. The half-life of fenpropathrin on the surface of a sterilized sandy loam was 3–4 days following irradiation with natural sunlight (Dureja 1990). After 15 days, it was observed that only about 12% of the original amount remained (Dureja 1990).

A mid-summer field study in Alberta, Canada was performed to determine the persistence of deltamethrin on crops and litter in order to establish a minimum time interval between treatment of pastures and grazing by cattle (Hill and Johnson 1987). The average half-life of deltamethrin applied to two pastures to control grasshoppers was 5.8 days on the forage and 17 days on the litter (Hill and Johnson 1987). The authors attributed the rapid initial loss of deltamethrin to surface processes including volatilization and photolysis, but the remainder of the loss occurred by degradation through metabolic and chemical processes. The longer half-life of deltamethrin on the litter reflects a lower initial loss of the chemical through surface processes (volatilization and photolysis) due to the litter being more sheltered.

No data exist regarding the degradation rates of pyrethrins in soil. Based upon hydrolysis and biodegradation studies of structurally similar esters and the relatively rapid degradation rates of the pyrethroids, it has been concluded that pyrethrins should degrade rapidly in soil (Crosby 1995).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Pyrethrins and pyrethroids have been detected at low levels in ambient air, indoor air samples, surface water, groundwater, and drinking water. These compounds have also been detected in soils, sediment, various foods, and animals. Quantitative concentration information is presented in the following sections.

6.4.1 Air

Pyrethrins and pyrethroids are used in both indoor and outdoor settings to control insects; therefore, these compounds are frequently detected in the air of homes and buildings after their use. During a study of pesticide use in Florida, permethrin was qualitatively identified in the porch or patio of two out of eight homes in Jacksonville, Florida during August of 1985 (Lewis et al. 1988). During a study of pesticide occurrence in indoor air of New Jersey households, permethrin was detected at concentrations of 2,550 ng/g (cis) and 3,850 ng/g (trans) in household dust immediately following its application as an aerosol flea treatment (Roinestad et al. 1993). The concentrations decreased to 550 ng/g (cis) and 675 ng/g (trans) 8 weeks postapplication. Permethrin, resmethrin and cypermethrin were detected in the ambient air of commercial pest control buildings in North Carolina at concentration ranges of 0.03–2.34, 0.31–14.10, and 0.02–11.66 μg/m^3, respectively (Wright et al. 1996). The concentration of cypermethrin detected in the air of vacant dormitory rooms following its application for cockroach control were 18.2, 8.5, 3.0,7.1, 4.4, 0.6, and 0.3 μg/m^3 at 0, 7, 28, 42, 56, 70, and 84 days postapplication, respectively (Wright et al. 1993). The concentration in untreated rooms adjacent to the sprayed rooms ranged from 0.1 μg/m^3 (84 days postapplication) to 6.4 μg/m^3 (immediately following application). The indoor air concentration of allethrin in a public community college cafeteria after bi-monthly applications ranged from 0.2 ng/m^3 (13 days after application) to 48 ng/m^3 (0.1 days after application) (Eitzer 1991). The maximum airborne residues of fenpropathrin in greenhouse air after application was 0.28 μg/m^3 (Siebers and Mattusch 1996).

The mean and maximum concentrations of vapor-phase fenpropathrin in air collected at Colmar, France between 1991 and 1993 were 0.5 and 2.7 ng/mL, respectively (Millet et al. 1997), while the mean and maximum concentrations of particulate-phase fenpropathrin in air were 0.6 and 4 ng/mL, respectively (Millet et al. 1997). The concentrations of permethrin and cypermethrin in airborne particulate matter in areas of Saudi Arabia with heavy insecticide use were 1.84–30.70 and 0.28–3.61 $\mu g/m^3$, respectively (Badawy 1998).

6.4.2 Water

Permethrin was detected in 24 of 12,253 ambient surface water samples in the United States at an average concentration of 0.0137 μg/L (EPA 2000c). Permethrin was detected 6 hours postapplication at concentrations of 0.017 and 0.018 μg/L in 2 of 6 samples from a slow-moving creek approximately 60 meters from a potato field where permethrin was applied via aerial spraying (Frank et al. 1991). Concentrations as high as 0.28 μg/L were observed 10 minutes postapplication, but decreased rapidly. In 1996, the average permethrin concentration in surface waters from agricultural areas in Thailand was 2.81 μg/L (Thapinta and Hudak 2000). The deposition of cypermethrin on the surface of three streams adjacent to vineyards in France that were sprayed (via mistblowers) with cypermethrin were in the range of 0.04–0.45 mg/m^2 and cypermethrin concentrations in subsurface water of the streams were in the range of 0.4–1.7 μg/L soon after spraying, but decreased to <0.1 μg/L within a period of about 5 hours (Crossland et al. 1982).

Since pyrethrins and pyrethroids adsorb strongly to soils, they are not often detected at elevated concentrations in groundwater and drinking water. In an EPA compilation of monitoring studies of pesticides in groundwater from 1971 to 1991, fenvalerate was detected in 5 out of 345 wells at concentrations of 0.01–0.28 μg/L and permethrin was detected in 4 out of 1,097 wells at concentrations of 0.01–1.25 μg/L (EPA 1992). Cypermethrin was not detected in 311 wells sampled, tralomethrin was not detected in 188 wells sampled and pyrethrins were not detected in 144 wells sampled (EPA 1992). As part of the National Drinking Water Contaminant Occurrence Database, permethrin was detected in 3 of 73 ambient spring water samples at an average concentration of 0.0133 μg/L and in 3 of 5,728 ambient groundwater samples at an average concentration of 0.011 μg/L (EPA 2000c). Permethrin was not detected in 94 wells analyzed in a 1992 USGS study of pesticides in near-surface aquifers in the Midwest (Kolpin et al. 1995). In the 1993–1995 USGS survey of pesticides in shallow groundwater throughout the United States, permethrin was detected in 2 out of 1,034 sites at a maximum concentration of 0.007 μg/L (Kolpin et al. 1998).

6.4.3 Sediment and Soil

Pyrethrins and pyrethroids are detected in agricultural soils or sediment from lakes, rivers, and streams that may have been contaminated from spray drift or runoff water. Following the application of a multi-purpose insecticide containing pyrethrins on a field in Franklin County Kentucky, the concentrations of pyrethrin I and II decreased in the soil as a function of time. After 1 hour, 1, 4, 8, 12, 18, 24, and 30 days, the concentrations of pyrethrin I were 9, 5.1, 3.9, 2.1, 0.9, 1.3, 0.3, and 0.8 μg/kg, respectively (Antonious et al. 1997). The concentrations of pyrethrin II over the same time frame were 900, 140, 103, 23, 1, 1, 1, and 1 μg/kg. The average concentration of permethrin in soils collected from 48 agrochemical facilities located throughout the state of Illinois was 190 μg/kg, with a range of concentrations from 11 to 4.22×10^5 μg/kg (Krapac et al. 1995). During 1996–1997, concentrations of permethrin in soil samples from cultivated areas in Thailand ranged from 62.41 to 1,178.40 μg/kg (Thapinta and Hudak 2000). Fenvalerate was detected in soil samples of 2 fields near the Nicolet River Basin in Quebec, Canada at concentrations of 20 and 8 μg/kg (0–5 cm depth) and 2 and 5 μg/kg (25–30 cm depth) (Caux et al. 1996). Permethrin was detected in the soil of two potato farms in Canada at concentrations ranging from 110 to 380 μg/kg at 6 hours after application via aerial spraying (Frank et al. 1991). The concentrations decreased to 6–220 μg/kg at 6 days postapplication and 8–15 μg/kg at 30 days postapplication (Frank et al. 1991).

Permethrin was detected in three of six sediment samples at concentrations of 18.1–21.1 μg/kg from a creek approximately 60 meters from a potato field where permethrin was applied via aerial spraying (Frank et al. 1991). At 30 days postapplication, permethrin was detected in only one of six samples at a concentration of 10 μg/kg (Frank et al. 1991). Sediment samples from an industrialized area of the Meltham Catchment in England contained permethrin at concentrations of 0.26–309.5 μg/kg and cyfluthrin at concentrations of 0.086–5.8 μg/kg (Yasin et al. 1996). Deltamethrin was detected in sediment samples of the Vemmenhog Catchment in Sweden at an average concentration of 20 μg/kg (Kreuger et al. 1999).

6.4.4 Other Environmental Media

According to the 1999 Food and Drug Administration (FDA) Pesticide Monitoring Program, permethrin was identified in 54 out of 1,040 food composites analyzed (FDA 2001). No range of levels was reported. Fenvalerate and fluvalinate were also qualitatively identified in food products, but no percentage of occurrence or concentrations were listed. Permethrin was also identified in 10 out of 78 baby foods at concentrations of 0.6–60 μg/kg and fenvalerate was identified in 1 out of 78 baby foods at a concentration of 5 μg/kg (FDA 2001). Resmethrin has been identified, but not quantified, in corn, cornmeal, flour, and wheat (Simonaitis and Cail 1975). An FDA analysis of 320 food groups conducted from 1991–1999 determined that pyrethroids were present at varying levels in several foods. The results of this study pertaining to pyrethroids are summarized in Table 6-3 (FDA 2000c).

Cypermethrin was detected in the milk from cows wearing ear tags impregnated with cypermethrin to control horn flies and other insects (Braun et al. 1985). Over a 21-day period, 60 milk samples were obtained from 10 cows. Only 11 out of 60 butterfat samples contained cypermethrin above the detection limit of 4 μg/kg. The range of concentrations in the butterfat of these 11 samples was 4.0–9.6 μg/kg (Braun et al. 1985). Flumethrin, deltamethrin, cypermethrin, and cyhalothrin were detected in the milk of 10 dairy cows after single dermal applications at recommended doses (Bissacot and Vassilieff 1997a). The highest mean concentration for flumethrin was observed 28 days postapplication, while the highest mean concentrations for cypermethrin and cyhalothrin were observed 1 day postapplication. The highest mean concentration of deltamethrin in the cows milk was observed 7 days postapplication.

Fenvalerate residues were detected in a variety of nontarget vertebrate and invertebrate species after application onto a cotton field to control bollworm and tobacco budworm (Bennet et al. 1983). Terrestrial invertebrates contained the lowest levels, while the highest residue concentrations were found in fish and insects. Fenvalerate levels in ppm were as follows: house mouse, 0.01; dickcissel, 0.02; ribbon snake, 0.12; toad, 0.02; golden shiner, 0.47; mosquitofish, 0.32; snail, 0.53; and ground beetle, 0.55 (Bennett et al. 1983).

Table 6-3. Levels of Pyrethroids Detected in Foods

Pyrethroid	Food Item	n	Mean (ppm)	Minimum (ppm)	Maximum (ppm)
Bifenthrin	Raw strawberries	3	0.0487	0.0040	0.084
Cyfluthrin	Green peppers	1	0.002	0.002	0.002
Cyfluthrin	Raw raddish	1	0.013	0.013	0.013
Cyfluthrin	Beef chow mein	1	0.004	0.004	0.004
Lambda cyhalothrin	Tomato sauce	1	0.003	0.003	0.003
Lambda cyhalothrin	Green peppers	1	0.01	0.01	0.01
Lambda cyhalothrin	Stuffed peppers	1	0.002	0.002	0.002
Cypermethrin	Broccoli	1	0.0013	0.0013	0.0013
Cypermethrin	Collards	7	0.442	0.052	1.247
Cypermethrin	Iceberg lettuce	2	0.0185	0.013	0.024
Esfenvalerate	Collards	4	0.0535	0.021	0.099
Esfenvalerate	Raw tomatoes	5	0.0146	0.005	0.02
Esfenvalerate	Green peppers	4	0.015	0.009	0.024
Esfenvalerate	Catsup	1	0.002	0.002	0.002
Esfenvalerate	Strained peaches/junior	2	0.0065	0.005	0.008
Esfenvalerate	Fruit dessert/junior	2	0.0025	0.002	0.003
Esfenvalerate	Raw apricot	1	0.06	0.06	0.06
Esfenvalerate	Mushrooms	1	0.019	0.019	0.019
Esfenvalerate	Stuffed peppers	3	0.005	0.003	0.007
Fenvalerate	Raw apricot	2	0.03	0.024	0.036
Fenvalerate	Strained peaches/junior	1	0.011	0.011	0.011
Fenvalerate	Red grapes	1	0.006	0.006	0.006
Fenvalerate	Raw cherries	1	0.11	0.11	0.11
Fenvalerate	Collards	12	0.1188	0.015	0.373
Fenvalerate	Raw tomatoes	4	0.0418	0.004	0.134
Fenvalerate	Green beans	2	0.017	0.015	0.019

Table 6-3. Levels of Pyrethroids Detected in Foods *(continued)*

Pyrethroid	Food Item	n	Mean (ppm)	Minimum (ppm)	Maximum (ppm)
Fenvalerate	Okra	1	0.032	0.032	0.032
Fenvalerate	Stuffed peppers	1	0.004	0.004	0.004
Fenvalerate	Tacos	1	0.002	0.002	0.002
Permethrin (cis)	Baked ham	1	0.001	0.001	0.001
Permethrin (trans)	Baked ham	1	0.001	0.001	0.001
Permethrin (cis)	Fried eggs	1	0.001	0.001	0.001
Permethrin (trans)	Fried eggs	1	0.0006	0.0006	0.0006
Permethrin (cis)	Dry roasted peanuts	1	0.006	0.006	0.006
Permethrin (trans)	Dry roasted peanuts	1	0.009	0.009	0.009
Permethrin (cis)	Popcorn	1	0.007	0.007	0.007
Permethrin (trans)	Popcorn	1	0.007	0.007	0.007
Permethrin (cis)	Rye bread	2	0.0099	0.0008	0.019
Permethrin (trans)	Rye bread	2	0.0109	0.0007	0.021
Permethrin (cis)	Raw peaches	3	0.0107	0.006	0.018
Permethrin (trans)	Raw peaches	3	0.014	0.006	0.027
Permethrin (cis)	Raw cantaloupe	2	0.045	0.004	0.005
Permethrin (cis)	Raw cherries	1	0.022	0.022	0.022
Permethrin (trans)	Raw cherries	1	0.022	0.022	0.022
Permethrin (cis)	Dried prunes	1	0.002	0.002	0.002
Permethrin (trans)	Dried prunes	1	0.002	0.002	0.002
Permethrin (cis)	Spinach	22	0.6283	0.003	2.31
Permethrin (trans)	Spinach	22	0.6803	0.002	2.74
Permethrin (cis)	Collards	22	0.3331	0.002	1.33
Permethrin (trans)	Collards	22	0.285	0.002	0.853
Permethrin (cis)	Iceberg lettuce	5	0.0104	0.0009	0.036
Permethrin (trans)	Iceberg lettuce	5	0.009	0.0009	0.034
Permethrin (cis)	Canned sauerkraut	1	0.0004	0.0004	0.0004

Table 6-3. Levels of Pyrethroids Detected in Foods *(continued)*

Pyrethroid	Food Item	n	Mean (ppm)	Minimum (ppm)	Maximum (ppm)
Permethrin (trans)	Canned sauerkraut	1	0.0005	0.0005	0.0005
Permethrin (cis)	Broccoli	10	0.0047	0.001	0.014
Permethrin (trans)	Broccoli	10	0.0037	0.0007	0.009
Permethrin (cis)	Raw celery	22	0.0113	0.001	0.031
Permethrin (trans)	Raw celery	22	0.0093	0.001	0.023
Permethrin (cis)	Asparagus	2	0.0862	0.0003	0.172
Permethrin (trans)	Asparagus	2	0.1087	0.0003	0.217
Permethrin (cis)	Cauliflower	1	0.004	0.004	0.004
Permethrin (trans)	Cauliflower	1	0.002	0.002	0.002
Permethrin (cis)	Raw tomato	16	0.0072	0.0006	0.015
Permethrin (trans)	Raw tomato	16	0.0072	0.0005	0.015
Permethrin (cis)	Green beans	1	0.005	0.005	0.005
Permethrin (trans)	Green beans	1	0.003	0.003	0.003
Permethrin (cis)	Green pepper	11	0.0332	0.005	0.081
Permethrin (trans)	Green pepper	11	0.0411	0.006	0.079
Permethrin (cis)	Raw raddish	1	0.001	0.001	0.001
Permethrin (trans)	Raw raddish	1	0.0005	0.0005	0.0005
Permethrin (cis)	Meatloaf	1	0.0006	0.0005	0.0006
Permethrin (trans)	Meatloaf	1	0.0006	0.0005	0.0006
Permethrin (cis)	Butter	1	0.002	0.002	0.002
Permethrin (trans)	Butter	1	0.003	0.003	0.003
Permethrin (cis)	Half & Half cream	1	0.0003	0.0003	0.0003
Permethrin (trans)	Half & Half cream	1	0.0005	0.0005	0.0005
Permethrin (cis)	Catsup	1	0.0009	0.0009	0.0009
Permethrin (trans)	Catsup	1	0.0007	0.0007	0.0007
Permethrin (cis)	Pumpkin pie	7	0.0024	0.0006	0.006
Permethrin (trans)	Pumpkin pie	7	0.0031	0.001	0.008

Table 6-3. Levels of Pyrethroids Detected in Foods *(continued)*

Pyrethroid	Food Item	n	Mean (ppm)	Minimum (ppm)	Maximum (ppm)
Permethrin (cis)	Chicken	1	0.001	0.001	0.001
Permethrin (trans)	Chicken	1	0.0008	0.0008	0.0008
Permethrin (cis)	Vegetables and chicken	1	0.001	0.001	0.001
Permethrin (trans)	Vegetables and chicken	1	0.001	0.001	0.001
Permethrin (cis)	Strained green beans/junior	2	0.0035	0.002	0.005
Permethrin (trans)	Strained green beans/junior	2	0.0035	0.002	0.005
Permethrin (cis)	Creamed spinach/junior	8	0.0372	0.0006	0.138
Permethrin (trans)	Creamed spinach/junior	8	0.0338	0.0004	0.12
Permethrin (cis)	Strained peaches/junior	14	0.0185	0.0006	0.078
Permethrin (trans)	Strained peaches/junior	14	0.022	0.0007	0.099
Permethrin (cis)	Strained pears/junior	3	0.0013	0.0008	0.002
Permethrin (trans)	Strained pears/junior	3	0.0009	0.0008	0.001
Permethrin (cis)	fruit dessert/junior	17	0.0045	0.0009	0.013
Permethrin (trans)	fruit dessert/junior	17	0.0057	0.0006	0.019
Permethrin (cis)	Veal cutlet	1	0.002	0.002	0.002
Permethrin (trans)	Veal cutlet	1	0.002	0.002	0.002
Permethrin (cis)	Wheat bread	1	0.0009	0.0009	0.0009
Permethrin (trans)	Wheat bread	1	0.0009	0.0009	0.0009
Permethrin (cis)	Canned peaches	1	0.0004	0.0004	0.0004
Permethrin (trans)	Canned peaches	1	0.0005	0.0005	0.0005
Permethrin (cis)	Canned tomatoes	3	0.0015	0.0004	0.002
Permethrin (trans)	Canned tomatoes	3	0.0016	0.0007	0.002
Permethrin (cis)	Brussel sprouts	12	0.0154	0.0004	0.127
Permethrin (trans)	Brussel sprouts	12	0.0124	0.0003	0.1
Permethrin (cis)	Mushrooms	6	0.0285	0.0003	0.159
Permethrin (trans)	Mushrooms	6	0.0221	0.0002	0.125
Permethrin (cis)	Turnips	1	0.001	0.001	0.001

Table 6-3. Levels of Pyrethroids Detected in Foods *(continued)*

Pyrethroid	Food Item	n	Mean (ppm)	Minimum (ppm)	Maximum (ppm)
Permethrin (trans)	Turnips	1	0.001	0.001	0.001
Permethrin (cis)	Okra	1	0.002	0.002	0.002
Permethrin (trans)	Okra	1	0.002	0.002	0.002
Permethrin (cis)	Beef stroganoff	1	0.018	0.018	0.018
Permethrin (trans)	Beef stroganoff	1	0.01	0.01	0.01
Permethrin (cis)	Stuffed peppers	9	0.0138	0.0005	0.074
Permethrin (trans)	Stuffed peppers	9	0.0171	0.0007	0.093
Permethrin (cis)	Tuna casserole	6	0.0014	0.0008	0.002
Permethrin (trans)	Tuna caracole	6	0.0012	0.0005	0.003
Permethrin (cis)	Quarter pound cheeseburger	1	0.005	0.005	0.005
Permethrin (trans)	Quarter pound cheeseburger	1	0.001	0.001	0.001
Permethrin (cis)	Tacos	3	0.0015	0.0004	0.003
Permethrin (trans)	Tacos	3	0.0018	0.0005	0.004
Permethrin (cis)	Pizza	2	0.0006	0.0004	0.0007
Permethrin (trans)	Pizza	2	0.0006	0.0003	0.0008
Permethrin (cis)	Beef chow mein	6	0.0016	0.0006	0.003
Permethrin (trans)	Beef chow mein	6	0.001	0.0006	0.002
Permethrin (cis)	Split peas with vegetables and ham	1	0.0008	0.0008	0.0008
Permethrin (trans)	Split peas with vegetables and ham	1	0.0009	0.0009	0.0009
Permethrin (cis)	Strained squash/junior	2	0.0009	0.0008	0.0009
Permethrin (trans)	Strained squash/junior	2	0.0009	0.0008	0.0009

Source: FDA 2000c

n = number of detections

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is currently exposed to pyrethrins and pyrethroids primarily from food sources, especially fruits and vegetables. The average daily intake (AVDI) of permethrin in units of ng/kg-body weight-per day in eight population groups was estimated using the FDA's monitoring program for chemical contaminants in the U.S. food supply. The data were obtained from the FDA Total Diet Studies conducted in 1982–1984 (Gunderson 1988), 1984–1986 (Gunderson 1995a), and 1986–1991 (Gunderson 1995b) and are summarized in Table 6-4. These values can be used to derive a rough estimate for the AVDI for all pyrethrins and pyrethroids because permethrin is the pyrethroid found most often in foods (see Table 6-3).

Many household products used to control insects, such as aerosol bombs, spray insecticides, and pet shampoos contain pyrethrins and pyrethroids, and therefore, dermal and inhalation exposures are possible. Because of the low mobility of these compounds in soil surfaces, pyrethrins and pyrethroids are rarely detected at elevated levels in drinking water or groundwater, with the exception of shallow wells near agricultural areas.

Occupational exposure to pyrethrins and pyrethroids will occur by inhalation and dermal contact with these compounds at workplaces where they are produced or used. The National Institute of Occupational Safety and Health (NIOSH) has conducted National Occupational Exposure Surveys (NOES) for pyrethrum and selected pyrethroids (NIOSH 1989). The NOES data do not include farm workers who are likely to be exposed to these compounds. Therefore, the estimated occupational exposures reported are likely to be greatly underestimated. Furthermore, these surveys were conducted prior to the development of many of the more recent pyrethroids and no current surveys exist. NIOSH (NOES 1981–1983) has statistically estimated that 11,296 total workers (1,537 of these are females) are exposed to pyrethrum in the United States (NIOSH 1989). Similarly, NIOSH has statistically estimated that 9,244 workers (1,758 of these are female) are potentially exposed to tetramethrin in the United States, and 27,596 workers (3,998 of these are female) are potentially exposed to resmethrin in the United States (NIOSH 1989). The NOES database does not contain information on the frequency, level, or duration of the exposure of workers to any of the chemicals listed therein. They are surveys that only provide estimates of workers potentially exposed to the chemicals.

Table 6-4. Average Daily Intake (AVDI, ng/kg/day) of Permethrin in Eight Population Groups

Date	Infants (6–11 months)	Toddlers (2 years)	14–16-year-old females	14–16-year-old males	25–30-year-old females	25–30-year-old males	60–65-year-old females	60–65-year-old males
1982–1984[a]	1.2	5.6	3.3	3.0	5.0	4.1	6.5	5.4
1984–1986[b]	89	25	10.7	14.9	15.1	13.7	24.2	22.4
1986–1991[c]	46.5	70.7	35.7	41.5	56.5	46.0	58.6	59.2

[a]Gunderson 1988
[b]Gunderson 1995a
[c]Gunderson 1995b

The concentration of 3-phenoxybenzoic acid (3-PBA), a urinary metabolite of permethrin, was measured in the urine of an agricultural worker exposed to this pyrethroid during its application to cabbage plants (Asakawa et al. 1996). The concentration of 3-PBA was 2.9 ng/mL (6 hours postapplication), 5.1 ng/mL (the morning after application), and 1.4 ng/mL (3 days postapplication) (Asakawa et al. 1996). Even though the worker was covered by protective clothing, it was determined that permethrin permeated the workers clothing and led to significant dermal exposure, particularly on the arms and legs (Asakawa et al. 1996). In a study of 50 workers applying deltamethrin and fenvalerate onto cotton fields, it was determined that dermal exposure represented the main route of exposure for the workers. Inhalation exposure rates were determined to be on the order of µg/hour, while dermal exposure was on the order of mg/hour (Zhang et al. 1991). Dermal exposure to deltamethrin for a pilot applying the insecticide on crops while flying an ultra-light aircraft was estimated as 10.8 µg/hour (Yoshida et al. 1990). A ground-based flagman on duty during the aerial spraying received an estimated dermal exposure of 25.4 µg/hour and dermal exposure to workers manually spraying deltamethrin was 2,800–65,400 µg/hour (Yoshida et al. 1990). The 1,000-fold exposure difference between hand-held applicators and aerial applicators was due, in part, to work practices of the workers. Dermal exposures on different regions of the bodies of workers who sprayed cypermethrin in tea plantations were measured (Wan 1990). Exposures (in µg/100 cm^2) were as follows: face: 0.06–0.72; chest: 0.11–2.06; abdomen: 0.09–2.68; thigh: 0.41–17.3; and ankle: 0.15–32.6. Total dermal exposures based upon spray amounts was 186–1,140 mg/kg for nonhand areas and 46.1 mg/kg for hands only (Wan 1990). Dermal exposure to permethrin was shown to be far greater than inhalation exposure for applicators involved in the spraying of this pyrethroid onto tomatoes in greenhouses (Adamis et al. 1985). The estimated respiratory exposure rate for these workers was 0.004 mg/hour and the dermal exposure rate was 3.8 mg/hour (Adamis et al. 1985). However, based upon the findings of animal studies, the absorption of pyrethroids is likely to be higher via oral and inhalation pathways when compared to dermal absorption (Eadsforth et al. 1988; van der Rhee et al. 1989; Woollen et al. 1992). Estimates of pyrethroid absorption in humans following dermal application range from about 0.3 to 1.8% of the administered dose (see Section 3.4).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children are exposed to pyrethrins and pyrethroids by similar routes that affect adults. Ingestion of foods is the most important exposure pathway for children. The AVDI of permethrin has been reported as 46.5 ng/kg-body weight/day for 6–11-month-old infants and 70.7 ng/kg-body weight/day for 2-year-old toddlers (Gunderson 1995b). No measurements have been made of these compounds in amniotic fluid, meconium, cord blood, neonatal blood or any other tissues that may indicate prenatal exposure. No data have been reported on the levels of pyrethrins or pyrethroids in breast milk.

The tendency of young children to ingest soil, either intentionally through pica or unintentionally through hand-to-mouth activity, is well documented. These behavioral traits can result in ingestion of pyrethrins and pyrethroids present in soil and dust. Since these compounds are adsorbed strongly to soils, they may not be in a highly bioavailable form. Young children often play on the ground or on carpets and this will increase the likelihood of dermal exposure and inhalation of contaminated particles from soil, household dust and treated surfaces. The transfer of allethrin residues from a carpeted floor to human subjects wearing dosimeter clothing was studied (Ross et al. 1990). For gloves, socks, shirts, and tights of subjects performing standardized aerobic exercises, the transfer coefficient ranged from 2.8 to 34.3 μg allethrin/cm^2 clothing for a period of up to 12.5 hours after applying allethrin (via foggers) to the carpet. The transfer rates decreased with time after application (Ross et al. 1990). Pyrethrins and pyrethroids are also frequently used in products such as pet shampoos or sprays, and since children often spend a great deal of time playing with pets, this can increase childhood exposure. Pyrethrins and certain pyrethroids have been employed in head lice treatment products, which are often used on children. Very little data were located regarding the concentrations of pyrethroids in milk and dairy samples. No pyrethroids were detected in any milk or dairy samples from the FDA Market Basket Surveys compiled from the 1991 to 1999 data (FDA 2000c). However, cypermethrin was detected in the milk from cows wearing ear tags impregnated with cypermethrin to control certain insects (Braun et al. 1985). Flumethrin, deltamethrin, cypermethrin, and cyhalothrin were detected in the milk of cows after single dermal applications (Bissacot and Vassilieff 1997a). Children may be exposed to pyrethrins and pyrethroids from the clothing of parents who work as pesticide applicators. Asakawa et al. (1996) documented that permethrin adhered to a worker's clothing and different parts of the body following the application of this insecticide onto a cabbage field. Similar findings were obtained for cotton sprayers using deltamethrin and fenvalerate (Zhang et al. 1991). Washing the affected clothing does not necessarily assure that all of the pyrethroids will be removed from the contaminated garments. Fabrics that simulated the clothing worn by workers applying cypermethrin insecticides were found to contain 1.7–2.3 μg/cm^2 before laundering; and after laundering, levels of 0.3–1.1 ng/cm^2 remained in the fabric (Laughlin et al. 1991). A study was conducted to determine the ability of laundry practices used by farm families to remove pesticides from clothing (Rigakis et al. 1987). After one wash, 2–18% of initial deltamethrin remained on fabrics, after two washes, 1–10% of initial deltamethrin remained on fabrics (Rigakis et al. 1987). Pretreating the fabric with a prewash spot removal product especially formulated to assist in the removal of oily stains resulted in the lowest recoveries. Cotton strips were coated with deltamethrin and then rinsed in deionized water for 1 hour (Hussain and Perschke 1991). After 4 rinses, only 37.7% of the initial deltamethrin was removed from the cotton. Impregnating the cotton with various paraffin wax and oils (corn, linseed, silicone) before coating with deltamethrin resulted in even lower percentages removed when washed (9.9–29.2% removal).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Aside from agricultural workers or insect control applicators, populations with potentially high exposures to pyrethrins or pyrethroids are small. Workers involved in the manufacturing and production of these insecticides are likely to be exposed to higher levels than the general population. Veterinarian professionals or pet groomers who frequently apply pyrethrin- and pyrethroid-containing shampoos or flea applications to animals may also be exposed to high levels of these compounds through dermal routes. Persons residing near farms or orchards may be subject to spray drift following application of these insecticides onto crops. Humans who use shampoos or sprays that contain pyrethrins or pyrethroids for their pets are likely to be exposed to higher levels of these compounds than persons without pets. Home gardeners who use pyrethroids and pyrethrins for insect control either in the garden or within the household itself may be exposed to high levels. Diet is also a key factor in relative human exposure level to pyrethrins and pyrethroids. As shown in Table 6-3, these compounds are frequently detected at varying levels in fruits and vegetables.

Permethrin is part of the United States Department Of Defense (DOD) Insect Repellent System and was issued in the Persian Gulf War to military personnel as a ready to use insect repellent for clothing application. It is also labeled for use on battle dress clothing and bed netting (Cecchine et al. 2000). Phenothrin was also used for spraying on bed netting and inside of aircrafts to prevent transport of insects. Due to an absence of sampling data and information about pesticide application rates, individual exposures were reconstructed by means of interviews with service personnel. The DOD reported that approximately 44 and 28% of all service personal in the Gulf used permethrin and phenothrin sprays, respectively, and that the guidelines for their recommended use were not always strictly adhered to (DOD 2001). This may have led to excessive exposures to these insecticides by some members of the military serving in the Persian Gulf.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of pyrethrins and pyrethroids are available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of pyrethrins and pyrethroids.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. As illustrated in Tables 4-4 and 4-5, the relevant physical and chemical properties of pyrethrins and the pyrethroids that are used in the United States are not entirely known. There are several pyrethroids that have been developed, and adequate data may not be available for all of them (Mueller-Beilschmidt 1990).

Production, Import/Export, Use, Release, and Disposal. Knowledge of a chemical's production volume is important because it may correlate with environmental contamination and human exposure. If a chemical's production volume is high, then there is an increased probability of general population exposure via consumer products and environmental sources, such as air, drinking water, and food.

The TRI99 (2001), which became available in 2001, has been used in this profile. The only pyrethroids that are on the list are allethrin, bifenthrin, cyfluthrin, cyhalothrin, fenpropathrin, fluvalinate, permethrin, phenothrin, resmethrin, and tetramethrin (TRI99 2001). Furthermore, data have only been reported for bifenthrin, cyfluthrin, permethrin, resmethrin, and tetramethrin. More detailed site- and medium-specific (e.g., air, water, or soil) release data for more pyrethroids are necessary. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1999, became available in 2001. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Information is available to permit assessment of the environmental fate and transport of the pyrethrins and pyrethroids in air (Chen and Casida 1969; Chen et al. 1984; HSDB 2001; Samsonov and Makarov 1996; Ueda et al. 1974), water (Maguire 1990; Rawn et al. 1982; Schimmel et al. 1983; USDA 2001a), and soil (Chapman et al. 1981; Hill 1983; Khan et al. 1988; Smith et al. 1995; USDA 2001a). Most of these compounds are rapidly degraded in the air by photolysis or through the reaction with oxidants such as hydroxyl radicals, ozone, or nitrate radicals found in the atmosphere. Many of the recently developed pyrethroids such as cyhalothrin are more stable towards sunlight than the early light sensitive pyrethroids like allethrin and resmethrin. Volatilization from water surfaces may be an important fate process for pyrethrins and pyrethroids with relatively large Henry's law constants, but adsorption to suspended solids and sediments will attenuate this process. Photolysis in sunlit surface waters has been demonstrated for several pyrethroids (Maguire 1990; Rawn et al. 1982; Schimmel et al. 1983). Hydrolysis is also an important environmental fate process in water or moist soil under alkaline conditions (Chapman and Cole 1982; USDA 2001a). Biodegradation occurs in water, soil, and sediment at varying rates (Cotham and Bidleman 1989; Hill 1983; Schimmel et al. 1983; Smith et al. 1995; USDA 2001a). Photolysis and volatilization of these compounds can occur on soil and plant surfaces (Hill and Johnson 1987; Takahashi et al. 1985a). These compounds are not expected to leach extensively since they have very little mobility in soils (USDA 2001a).

While it can be reasonably concluded that pyrethrins will biodegrade in the environment based upon their chemical structure, there are no specific biodegradation studies of the six pyrethrins. Furthermore, there are several synthetic pyrethroids for which experimental data regarding their biodegradation, bioconcentration, photolysis, adsorption, and hydrolysis are not available. Studies on these pyrethroids are warranted.

Bioavailability from Environmental Media. The bioavailability of pyrethrins and pyrethroids from contaminated air, water, soil, or plant material in the environment has not been adequately studied. Workers applying pyrethroids in the field have a much greater dermal exposure rate when compared to inhalation exposure (Adamis et al. 1985; Wan 1990; Yoshida et al. 1990; Zhang et al. 1991), but the percentage of pyrethroid absorbed dermally is less than oral and inhalation absorption (Eadsforth et al. 1988; van der Rhee et al. 1989; Woollen et al. 1992). Since these compounds adsorb strongly to soils, bioavailability from soil may be limited, but absorption and bioavailability studies of these compounds from soils are lacking. Studies are needed on the bioavailability of these compounds from actual environmental media and on differences in bioavailability for the various pyrethrins and pyrethroids.

Food Chain Bioaccumulation. Bioconcentration occurs in aquatic organisms (Freitag et al. 1985; Haitzer et al. 1998; Schimmel et al. 1983). There is no evidence to indicate that bioaccumulation occurs in aquatic or terrestrial species, but studies are needed to determine if pyrethrins and pyrethroids bioaccumulate up the food chain.

Exposure Levels in Environmental Media. Atmospheric concentrations of pyrethrins or pyrethroids are usually on the order of $\mu g/m^3$ immediately after their application (Eitzer 1991; Siebers and Mattusch 1996), but the levels decrease with time because these compounds undergo rapid degradation in the atmosphere. These compounds are infrequently detected in groundwater and drinking water in the United States because of their strong adsorption to soils and relatively rapid rate of degradation. Pyrethrins and pyrethroids are found in soils following their application, but their levels decrease with time. The average concentration of permethrin in soils collected from 48 agrochemical facilities located throughout the state of Illinois was 190 μg/kg (Krapac et al. 1995). More data regarding the levels of pyrethrins and pyrethroids in water and soil surfaces are needed in order to produce better estimates of the potential for human exposure to these compounds. Foods, especially fruits and vegetables, have been shown to contain pyrethroids at varying levels (Table 6-3). Continued monitoring data of these compounds in foods are necessary since ingestion of food sources is the most likely route of widespread human exposure.

Exposure Levels in Humans. The general population is exposed to pyrethrins and pyrethroids primarily through the ingestion of food sources. The AVDI of permethrin, the most frequently used pyrethroid in the United States, has been estimated for eight different population groups (Gunderson 1988, 1995a, 1995b). Additional data regarding the AVDI for other pyrethroids and pyrethrins would be useful in assessing total exposure for the U.S. population. The use of household insecticides containing these compounds can also lead to dermal and inhalation exposure. Workers employed in the agricultural industry, veterinary industry, or pet grooming business may be occupationally exposed to high levels of these compounds. Dermal exposure has been shown to be greater than inhalation exposure for applicators involved in the spraying of pyrethroids (Adamis et al. 1985; Wan 1990), but dermal absorption appears to be lower than the amount absorbed from the other routes. While body burden studies were located for persons occupationally exposed (Asakawa et al. 1996; Wan 1990), body burden studies are needed for the general population of the United States.

Exposures of Children. Estimates regarding the AVDI of permethrin for children are available (Gunderson 1988, 1995a, 1995b). Additional data regarding the AVDI for other pyrethroids and pyrethrins would be useful to assess childhood exposure more thoroughly. Body burden studies of children are also necessary. Since children may be exposed to these compounds from pica, bioavailability studies from soils would be useful for a wide array of pyrethrins and pyrethroids.

Child health data needs relating to susceptibility are discussed in Section 3.12.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for pyrethrins and pyrethroids were located. These substances are not currently amoung the compounds for which a subregistry has been established in the National Exposure Registry. The substances will be considered in the future when chemical selection is made for subregistries to be established. The information amassed in the National Exposure Registry facilitates epidemiological research needed to assess adverse health outcomes that may be related to exposure to pyrethrins and pyrethroids.

The development of a registry of exposures would provide a useful reference tool for monitoring exposure levels and frequencies over time. Such a registry would allow an assessment of the variations in exposure levels from various sources. Also it could be used to assess the effect of geographical, seasonal, or regulatory actions on the level of exposure from a certain source. These assessments, in turn, would provide a better understanding of the needs for research or data acquisition based on the current exposure levels.

6.8.2 Ongoing Studies

The Federal Research Programs In Progress (FEDRIP 2001), Current Research Information System (CRIS/USDA 2001), and Computer Retrieval of Information on Scientific Projects (CRISP 2001) databases indicates several projects are ongoing that may fill some existing data gaps. Symbiotech Inc. located in Wallingford, Connecticut is investigating a topical preparation of permethrin intended for use on humans as an insect repellent (FEDRIP 2001). Researchers at the University of Arkansas (Dr. Meisch and Dr. Bernhardt) are investigating the efficacy and environmental effects of various pyrethroids for mosquito control in riceland systems (CRIS/USDA 2001). Dr. Epstein from the University of California Davis, is developing software based on the California Department of Pesticide Regulation's Pesticide Use Reports to document trends in fungicide and insecticide use on grapes and almonds, respectively (CRIS/USDA 2001). Dr. Hammock from the University of California Davis is attempting to develop and validate single compound, as well as class selective immunoassays for urinary metabolites of hazardous compounds (including pyrethroids) for use as biomarkers of internal exposure to these compounds (CRISP 2001).

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring pyrethrins and pyrethroids, their metabolites, and other biomarkers of exposure and effect to pyrethrins and pyrethroids. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL SAMPLES

Exposure to pyrethrins and pyrethroids is most commonly evaluated by the analysis of urine and blood using gas chromatography (GC) combined with electron capture detection (ECD), flame ionization detection (FID), or mass spectrometry (MS) and high performance liquid chromatography (HPLC) coupled with ultraviolet (UV) detector. Recovery is generally high and sensitivity is in the parts per billion (ppb) range.

A simple and rapid method for the isolation of synthetic pyrethroids using a solid phase extraction method is described by Junting and Chichang (1991). A similar method that employs HPLC for analysis was used to quantify pyrethrins in plasma by Wintersteiger et al. (1994). This method eliminates time consuming repeated extractions with organic solvents and centrifugations without losing the efficiency of recovery.

Pyrethrins and pyrethroids are extensively metabolized by the cleavage of the ester linkage, oxidation, and conjugation. Metabolites formed are less lipophilic, and are rapidly and easily excreted in the urine. Exposure to pyrethrins and pyrethroids can be monitored by the detection of these excreted metabolites. Pyrethroids such as cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, fenvalerate, phenothrin, and permethrin can be metabolized resulting in the formation of halosubstituted chrysanthemic and 3-phenoxybenzoic acids (Angrer and Ritter 1997; Yao et al. 1992). The rapid metabolism of the pyrethroids makes it useful to monitor for pyrethroid metabolites in the urine of exposed individuals rather than monitoring the actual concentration of the pyrethroid itself in blood (Leng et al. 1999a). Also, it has been demonstrated that storing frozen urine samples for up to a year results in no further degradation of the metabolites (Leng et al. 1999a). In contrast, pyrethroids stored in plasma are susceptible to continued degradation (Leng et al. 1999a).

Methods for analyzing pyrethrins and pyrethroids as well as the metabolites in biological samples are shown in Table 7-1.

7.2 ENVIRONMENTAL SAMPLES

Concerns about contamination of environmental media, plants, and animals with pyrethrins have led to the need for more rapid, sensitive, and selective methods of analysis. As with biological samples, the most common methods of analysis are GC combined with ECD, FID, or flame photometric detection (FPD) and HPLC coupled with UV detector. Thermal conductivity detectors, thermionic detectors, and nitrogen phosphorus detectors have also been used in conjunction with GC.

Pyrethrins and pyrethroids are nonpolar compounds and nonsystemic in plants; thus, the extraction procedures in environmental samples are simpler than those used for organophosphate and carbamate insecticides. Generally, the samples are homogenized with a nonpolar solvent, such as hexane or benzene, or a binary solvent mixture such as hexane-acetone, hexane-isopropanol, or light petroleum-diethyl ether. The pyrethrins and pyrethroids, along with a wide variety of other lipophilic substances are co-extracted during this procedure. The resulting solution is dried with anhydrous sodium sulphate. If there are too many co-extracted compounds, separation by liquid-liquid partition or column chromatography is performed. Samples with a low water content, such as tea, tobacco, and straw, are usually extracted with a binary solvent mixture, as are moist vegetables and fruits. Soil samples are first ground and filtered to remove large particles and stones, and then are extracted with acetone-hexane, methanol, acetone, or acetonitrile. Pyrethrins and pyrethroids are extracted from water samples with hexane, methylene chloride, or acetonitrile with subsequent drying with anhydrous sodium sulphate.

In the analysis of pyrethrins, the total residues of the six active compounds are often analyzed for, but in the analysis of pyrethroids, the individual compounds are usually quantified (Chen and Wang 1996). An extensive review of the chromatographic methods employed for the determination of pyrethrins and

Table 7-1. Analytical Methods for Determining Pyrethrins and Pyrethroids in Biological Materials

Sample matrix	Analyte	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood, milk	Deltamethrin, cyhalothrin cypermethrin, flumethrin	Acidify with 1 N HCl; extract twice with CH_3CN and filter; extract filtrate with hexane and discard the hexane phase; remove CH_3CN under a stream of N_2 and heat to dryness; cleanup on a silica gel column; dissolve in CH_3CN and filter through a 0.45 μm pore cellulose filter	LC/UV	1.0 μg/kg	78–91	Bissacot and Vassilieff 1997a, 1997b
Plasma	Pyrethrins	Dilute centrifuged plasma with water; cleanup on a solid phase extraction column; elute with methanol	RPHPLC/UV	0.167 mg/L	70–72	Wintersteiger et al. 1994
Plasma	Cyfluthrin, cypermethrin, permethrin	Precipitation of proteins followed by liquid-liquid extraction	GC/ECD	5 μg/L	No data	Leng et al. 1999a
Plasma, urine	Fenopropathrin, permethrin, cypermethrin, fenvalerate, deltamethrin	Mix samples with 70% methanol; pour on to Sep-Pak C_{18} columns pretreated with chloroform, methanol, methanol/water, and water; wash with water; elute with chloroform; evaporate to dryness under stream of N_2; redissolve in ethanol	GC/FID	2 mg/L	81–93 90–102	Junting and Chuichang 1991
Urine	Cis- and trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cycloprane-1-carboxylic acid; 3-phenoxybenzoic acid; fluorophenoxybenzoic acid	Liquid-liquid extraction followed by methylation of the free acid metabolites	GC/MS	0.5 μg/L	No data	Leng et al. 1999b

Table 7-1. Analytical Methods for Determining Pyrethrins and Pyrethroids in Biological Materials *(continued)*

Sample matrix	Analyte	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Cis- and trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cycloprane-1-carboxylic acid; cis-3-(2,2-dibromovinyl)-2,2-dimethylcycloprane-1-carboxylic acid; 3-phenoxy-benzoic acid; 4-fluoro-3-phenoxy-benzoic acid	Acidify with AcOH; add concentrated H_2SO_4; heat at 90 °C for 1 hour; cleanup on C_{18} column; elute with methanol into a vial containing concentrated H_2SO_4; complete derivatization on water bath for 1 hour; extract with hexane	GC/MS	0.3–0.5 μg/L	90–98	Angerer and Ritter 1997
Urine	Dibromovinyl-dimethylcyclo-propane carboxylic acid, 3-phenoxybenzyl-hydroxy-ethyl acetate, 3-phenoxybenzoic acid	Adjust pH of sample to 6.5; extract with hexane; evaporate to dryness; redissolve in methanol	RPHPLC/UV	No data	95	Yao et al. 1992
Urine	Deltamethrin, fenvalerate	Extract with hexane; concentrate and cleanup on Florisil column; elute with benzene; dry on anhydrous Na_2SO_4	GC/ECD	0.2 μg/L	92–95.3	Yi-Qun et al. 1994

AcOH = acetic acid; CH_3CN = acetonitrile; ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatography; HCl = hydrochloric acid; H_2SO_4 = sulfuric acid; LC = liquid chromatography; MS = mass spectrometry; N_2 = nitrogen; Na_2SO_4 = sodium sulfate; RPHPLC = reverse phase high performance liquid chromatography; UV = ultra-violet detection pyrethroids in foods, crops, and environmental media has been published (Chen and Wang 1996). Many pyrethroids such as bifenthrin, cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, fenvalerate, and permethrin possess one or more halogenated atoms which are sensitive to ECD. Often, derivitization is used to create a sensitive group for pyrethroids that do not possess halogenated atoms (allethrin, resmethrin, phenothrin, and tetramethrin, for example), or to improve the sensitivity and peak tailing situations in some halogenated pyrethroids (Chen and Wang 1996). Consequently, GC/ECD is the most popular analytical approach for analyzing pyrethroids in environmental samples.

A detection limit of 0.1 μg/m^3 and a mean recovery of 100.15% has been reported for the analysis of cypermethrin in air using GC/ECD (Pomorska 1999), while permethrin and resmethrin had detection limits in the ng/m^3 and very good recoveries with a GC/MS method (Roinestad et al. 1993). This is comparable to methods used for the determination of other pyrethroids in air using GC (EMMI 1997). The analysis of pyrethrins and pyrethroids in water is also accomplished through the use of GC and HPLC. Detection limits in the ppb (μg/L) range have been achieved (EMMI 1997). A method for the analysis of selected pyrethroids in soils has been described by Alawi et al. (1990) that utilizes GC equipped with a nitrogen phosphorus detector (NPD).

Methods for analyzing pyrethrins in environmental samples are shown in Table 7-2.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of pyrethrins and pyrethroids are available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of pyrethrins.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

Table 7-2. Analytical Methods for Determining Pyrethrins and Pyrethroids in Environmental Samples

Sample matrix	Analyte	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Allethrin, fenvalerate, pyrethrin I, resmethrin	Air samples collected on a sorbent cartridge; extract with 5% diethyl ether in hexane	GC/ECD; GC/NPD; GC/FPD; HPLC/UV	0.1–50 μg/m^3	No data	ASTM D4861 EMMI 1997
Air	Cypermethrin	Air samples collected on a sorbent cartridge; extract with acetone	GC/ECD	0.1 μg/m^3	100.15 (mean recovery)	Pomorska 1999
Air	Resmethrin, permethrin	Air samples collected on filter paper or Tenax tubes; extract with acetone	GC/MS	1 ng/m^3 (permethrin); 10 ng/m^3 (resmethrin)	109.5–110.9 (permethrin); 84.6 (resmethrin)	Roinestad et al. 1993
Air (dust)	Resmethrin, permethrin	Dust samples are homogenized in a blender or food processor; extract with acetone	GC/MS	50 ng/g (permethrin); 100 ng/g (resmethrin)	94.8–124.4 (permethrin); 82.6 (resmethrin)	Roinestad et al. 1993
Air	Pyrethrums	Air samples collected with sampling pump equipped with filter; extract with CH_3CN	HPLC/UV	mg/m^3	No data	NIOSH 5008 EMMI 1997
Fats, oils, milk, cheese, fish	Allethrin, bifenthrin, deltamethrin, esfen-valerate, fenvalerate, permethrin, tetramethrin, tralomethrin	Dissolve fat in petroleum ether; extract with CH_3CN; dilute with water; clean up on Florisil column; extract with petroleum ether/ethyl ether	GC/ECD	No data	No data	FDA 211.1; FDA 231.1 EMMI 1997
Fatty and non fatty foods	Allethrin, bifenthrin, cyfluthrin, deltamethrin, esfenvalerate, fenpropathrin, fenvalerate, fluvalinate, permethrin, tetra-methrin, tralomethrin	Dissolve fat in petroleum ether; extract with CH_3CN; dilute with water; cleanup on Florisil column; elute with a series of eluants—methylene chloride, hexane, and CH_3CN	GLC/ECD	No data	No data	FDA 252 EMMI 1997

Table 7-2. Analytical Methods for Determining Pyrethrins and Pyrethroids in Environmental Samples *(continued)*

Sample matrix	Analyte	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Non-fatty foods	Allethrin, bifenthrin, cyfluthrin, deltamethrin, esfenvalerate, fenpropathrin, fenvalerate, fluvalinate, permethrin, tetra-methrin, tralomethrin	Extract with CH_3CN or CH_3CN/water mixture; dilute with water; extract with petroleum ether; cleanup on Florisil column; elute with petroleum ether/ethyl ether	GC/FPD	No data	No data	FDA 232.1 EMMI 1997
Non-fatty food	Bifenthrin, cyfluthrin, deltamethrin, esfenvalerate, fenvalerate, flucythrinate, fluvalinate, permethrin	Blend with acetone and filter; extract with petroleum ether and methylene chloride; concentrate to remove methylene chloride	GC/ECD; GC/FPD	No data	No data	FDA 232.4 EMMI 1997
Non-fatty food	Deltamethrin, fenpropathrin, tralomethrin	Blend with acetone and filter; extract with methylene chloride; cleanup on a column containing charcoal, MgO, and Celite 545; elute with CH_3CN-benzene	GC/FPD; GC/TSD	No data	No data	FDA 232.3 EMMI 1997
Fruits, vegetables, grains	Bifenthrin, cyhalothrin, cypermethrin, delta-methrin, fenpropathrin, fenvalerate, fluvalinate, permethrin	Homogenize in CH_3CN and filter; extract with hexane; wash with 4% NaCl; dry over anhydrous Na_2SO_4; evaporate to dryness; redissolve in hexane; extract with CH_3CN; evaporate to dryness; redissolve in hexane; cleanup on Florisil column; elute with a mixture of petroleum ether and ethyl ether.	GC/ECD	No data	>70	Pang et al. 1997
Ground-water, drinking water	Permethrin	Extract with methylene chloride; dry over anhydrous Na_2SO_4; concentrate; add methyl tert-butyl ether	GC/ECD	0.5 μg/L	No data	EMSLC 508 EMMI 1997

Table 7-2. Analytical Methods for Determining Pyrethrins and Pyrethroids in Environmental Samples *(continued)*

Sample matrix	Analyte	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Waste water, municipal and industrial	Allethrin, cyfluthrin, fenvalerate, phenothrin, pyrethrins I, pyrethrins II, resmethrin, tetramethrin	Saturate sample with NaCl; extract with CH_3CN; concentrate extract	HPLC/UV	2 μg/L	No data	EAD 1660 EMMI 1997
Waste water, industrial	Resmethrin	Extract with methylene chloride; dry over anhydrous Na_2SO_4; concentrate	GC/FID	36 μg/L	No data	EMSLC 616 EMMI 1997
Soil	Cypermethrin, permethrin, cyfluthrin, fluvalinate, deltamethrin	Extract with acetone saturated with sodium chloride; dry with Na_2SO_4	GC/NPD	0.004–0.012 mg/kg	114	Alawi et al. 1990
Pet shampoo	Pyrethrins I, pyrethrins II, tetramethrin	Dilute with water and add Celite 545; add to a Celite column; elute with petroleum ether; filter through 0.5 μm filter	HPLC/UV GC/FID	No data	No data	EPA-B EMMI 1997
Pesticide formulation	Pyrethrins I, pyrethrins II	Extract with petroleum ether; filter; evaporate the filtrate to <1 mL; add 0.5 N alcoholic NaOH and reflux gently; concentrate; add Filter-Cel and 10% $BaCl_2$ filter; neutralize with H_2SO_4 using phenolphthalein; extract with petroleum ether; extract with 0.1 N NaOH; add Deniges reagent and let stand in darkness; add alcohol and precipitate HgCl with NaCl solution; filter; add dilute HCl; add chloroform and ICl solution	Titration	No data	No data	AOAC 936.05 EMMI 1997
Pesticide formulation	Permethrin	Dissolve in methyl isobutyl ketone	GC/FID	No data	No data	AOAC 986.03 EMMI 1997
Pesticide formulation	Deltamethrin	Dissolve (and sonicate) in isooctane-1,4-dioxane; filter	HPLC/UV	No data	No data	AOAC 991.03 EMMI 1997

Table 7-2. Analytical Methods for Determining Pyrethrins and Pyrethroids in Environmental Samples *(continued)*

Sample matrix	Analyte	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Pesticide formulation	Allethrin	Add ethylenediamine; swirl; let stand; wash with pyridine; add thymophthalein indicator; titrate with 0.1 N NaOMe	Titration	No data	No data	AOAC 953.05 EMMI 1997
Pesticide formulation	Pyrethrums	Dilute with acetone; add dicyclohexyl phthalate (internal standard)	GC/FID	No data	No data	AOAC 982.02 EMMI 1997
Pesticide formulation	Pyrethrins I, pyrethrins II	Add sample to a column packed, bottom to top, with anhydrous Na_2SO_4, Florisil, and anhydrous Na_2SO_4; wash with hexane; elute with acetone; evaporate to dryness; dissolve residue in carbon disulfide; dry over anhydrous Na_2SO_4	GC/FID	No data	No data	EPA-B EMMI 1997
Aerosol formulation	Resmethrin	Cool can in freezer overnight; punch holes in can to relieve pressure; open can and warm to room temperature; remove remaining volatiles by placing in a water bath; dissolve residue in benzene	GC/TCD	No data	No data	PMD-Res EMMI 1997
Aerosol formulation	Resmethrin	Cool can in freezer overnight; punch holes in can to relieve pressure; open can and warm to room temperature; remove remaining volatiles by placing in a water bath; dissolve residue in methanol	RPHPLC/ UV	No data	No data	PMD-Res EPA-B EMMI 1997

BaCl = barium chloride; CH_3CN = acetonitrile; ECD = electron capture detector; FID = flame ionization detector; FPD = flame photometric detector; GC = gas chromatography; HCl = hydrochloric acid; HgCl = mercuric chloride; HPLC = high performance liquid chromatography; H_2SO_4 = sulfuric acid; ICl =iodine mono-chloride; MgO = magnesium oxide; NaCl = sodium chloride; NaOH = sodium hydroxide; NaOMe = sodium methoxide; Na_2SO_4 = sodium sulfate; NPD = nitrogen phosphorus detector; RPHPLC = reverse phase high performance liquid chromatography; TCD = thermal conductivity detector; TSD = thermionic detector; UV = ultra-violet detection

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods for detecting and quantifying pyrethrins and pyrethroids in blood (Bissacot and Vassilief 1997a, 1997b), plasma (Junting and Chuichang 1991; Wintersteiger et al. 1994), and urine (Junting and Chuichang 1991; Yi-Qun et al. 1994) are available. Chromatographic techniques, such as GC and HPLC, were used to isolate pyrethrins and their degradation products. ECD, FID, UV, and MS were coupled with the separation techniques to detect these compounds. Sensitivity was high (blood: 1 μg/kg; plasma: 2–0.17 μg/kg; urine: 0.2–0.5 μg/L). These methods can accurately detect pyrethrins at background concentrations in blood, plasma, and urine. Methods are available to characterize the metabolites of selected pyrethroids in urine (Angrer and Ritter 1997; Leng et al. 1999a; Yi-Qun et al. 1994). The sensitivity is high and the recovery is good. The existing methods for detecting the pyrethrins in biological samples seem to be adequate.

Effect. Other than the clinical signs of Type I and Type II pyrethroid poisoning discussed in Section 3.8.2, there are no known biomarkers of effect for pyrethrins and pyrethroids. It is important to note that while these effects are characteristic signs of pyrethroid poisoning, they are not exclusive to pyrethroid poisoning. In humans, pyrethroids are rapidly metabolized by esterase, mainly in the liver, and it may be possible to correlate carboxylesterase activity with pyrethroid induced adverse effects (Leng et al. 1999b). However, human plasma contains very little carboxyesterases and the liver is not accessible for routine measurements. As a parameter of carboxyesterase activity for Type II pyrethroids, the production of cyanic acid in human lymphocytes was measured (Leng et al. 1999b). Initial findings indicate that the determination of carboxyesterase activity in lymphocytes may potentially be used as a marker for individual susceptibility.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods are available to measure pyrethrins in air (EMMI 1997; Pomorska 1999), foods (EMMI 1997), water (EMMI 1997), waste water (EMMI 1997), soil (Alawi et al. 1990), and in formulations (methods by American Society for Testing Materials [ASTM], NIOSH, Food and Drug Administration [FDA], Environmental Protection Agency [EPA], Environmental Measurements Laboratory Center [EMLC], Engineering and Analysis Division [EAD], AOAC). Sensitivity and recovery are not mentioned for several of the methods.

7.3.2 Ongoing Studies

Z. Elrassi, of Oklahoma State University, is conducting research on the development of high performance capillary electrophoresis (HPCE) and capillary elcetrochromatography (CEC) methods for the rapid, sensitive, and efficient separation of pesticides and their metabolites (CRIS 2001). B.W. Blair, of the Canadian Food Inspection Agency, Food Inspection Directorate, Lab Services Division, is developing a rapid, simple, and inexpensive immunological assay technology for low molecular weight contaminants of significance in food safety testing, as a tool for monitoring contaminants in foods and other environmental media (CRIS 2001).

In a study sponsored by the National Institute of Environmental Health Sciences at University of California, Davis, research is being performed to develop and validate single compounds, as well as a class selective immunoassay for urinary metabolites of hazardous compounds such as pyrethroids for use as biomarkers of internal exposure to theses compounds (CRISP 2001).

8. REGULATIONS AND ADVISORIES

Available information on international, national, and state regulations and standards of pyrethrins and pyrethroids is presented in Table 8-1. Information concerning tolerances for residues of pyrethrin and selected pyrethroids is presented in Table 8-2.

ATSDR has not derived acute-, intermediate-, or chronic-duration inhalation MRLs for pyrethrins or pyrethroids because adequate data were not available by this route of exposure.

ATSDR derived an acute-duration oral MRL of 0.0007 mg/kg/day for bioallethrin (Type I pyrethroid). This MRL is based on a LOAEL of 0.21 mg/kg/day for neurodevelopmental effects in mice. An uncertainty factor of 300 was used (10 for use of a LOAEL, 10 for animal to human extrapolation, and 3 to account for intrahuman variation) to derive the MRL.

ATSDR derived an acute-duration oral MRL of 0.002 mg/kg/day for deltamethrin (Type II pyrethroid). This MRL is based on a LOAEL of 0.7 mg/kg/day for neurodevelopmental effects in mice. An uncertainty factor of 300 was used (10 for use of a LOAEL, 10 for animal to human extrapolation, and 3 to account for intrahuman variation) to derive the MRL.

ATSDR has not derived intermediate or chronic oral MRLs for pyrethrins or pyrethroids because animal studies in which health effects were assessed following oral administration of various pyrethroids for intermediate or chronic durations identified LOAELs that were higher than the LOAELs of 0.021 and 0.7 mg/kg/day for neurodevelopmental effects in mice following acute-duration oral exposure to bioallethrin and deltamethrin, respectively.

Table 8-1. Regulations and Guidelines Applicable to Pyrethrins and Pyrethroids

Agency	Description	Information	References
<u>INTERNATIONAL</u>			
Guidelines:			
IARC	Carcinogenic classification Deltamethrin Fenvalerate Permethrin	Group 3[a]	IARC 2001
WHO	Drinking water guideline Permethrin	 20 μg/L	WHO 2001
<u>NATIONAL</u>			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV-TWA—pyrethrum	5 mg/m^3	ACGIH 2000
NIOSH	REL (TWA)—pyrethrum IDLH—pyrethrum	5 mg/m^3 5,000 mg/m^3	NIOSH 2001
OSHA	PEL (8-hour TWA)—pyrethrum General industry (total dust)	 5 mg/m^3	OSHA 2001a 29CFR1910.1000 Table Z-1
	PEL (8-hour TWA)—pyrethrum Construction industry (total dust)	 5 mg/m^3	OSHA 2001c 29CFR1926.55 Appendix A
	PEL (8-hour TWA)—pyrethrum Shipyard industry (total dust)	 5 mg/m^3	OSHA 2001b 29CFR1915.1000 Table Z
b. Water			
EPA	Water pollution; determination of reportable quantity—pyrethrin	1 pound	EPA 2001c 40CFR117.3
	Water pollution; designation of hazardous substance—pyrethrin		EPA 2001a 40CFR116.4
	NPDES; toxic pollutants and hazardous substances required to be identified by existing dischargers if expected to be present—pyrethrins		EPA 2001d 40CFR122 Appendix D

Table 8-1. Regulations and Guidelines Applicable to Pyrethrins and Pyrethroids *(continued)*

Agency	Description	Information	References
NATIONAL *(cont.)*			
c. Food			
FDA	Pyrethrins in combination with piperonyl butoxide may be safely used for insect control on bags intended for use in contact with dried food		FDA 2000a 21CFR178.3720
USDA	Labeling treated seed—"don't use for food, feed, or oil purposes"		USDA 2001b 7CFR201.31a(d)
	Pyrethrins		
	Oat	1 ppm	
	Sorghum	3 ppm	
d. Other			
ACGIH	Carcinogenicity classification—pyrethrum	A4[b]	ACGIH 2000
DOT	Superfund—reportable quantity		DOT 2001 49CFR172.101 Appendix A
	Pyrethrins	1 pound	
EPA	RfD (mg/kg/day)		IRIS 2001e
	Type I Pyrethroids		
	Biphenthrin	1.5×10^{-2}	
	Permethrin	5.0×10^{-2}	
	Resmethrin	3.0×10^{-2}	
	Type II Pyrethroids		
	Baythroid/Cyfluthrin	2.5×10^{-2}	
	Cyhalothrin/Karate	5.0×10^{-3}	
	Cypermethrin	1.0×10^{-2}	
	Danitol/Fenpropathrin	2.5×10^{-2}	
	Fluvalinate	1.0×10^{-2}	
	Pydrin/Fenvalerate	2.5×10^{-2}	
	Tralomethrin	7.5×10^{-3}	
	Superfund—reportable quantity		EPA 2001b 40CFR302.4
	Pyrethrins	1 pound	
	Toxic chemical release reporting; Community Right-to-Know—effective date		EPA 2001e 40CFR372.65
	Fenvalerate	01/01/95	
	Permethrin	01/01/95	

Table 8-1. Regulations and Guidelines Applicable to Pyrethrins and Pyrethroids *(continued)*

Agency	Description	Information	References
NATIONAL *(cont.)*			
FDA	New animal drug—for use in the treatment of ear mites in dogs and cats	0.05% pyrethrins	FDA 2000b 21CFR524.2140
STATE			
Regulations and Guidelines:			
a. Air			
Alaska	Air contaminant standard (TWA)		BNA 2001
	Pyrethrum	5 mg/m^3	
California	Airborne contaminant—pyrethrum		BNA 2001
Connecticut	HAP—pyrethrum		BNA 2001
Hawaii	Air contaminant—pyrethrum		BNA 2001
	PEL	5 mg/m^3	
	STEL	10 mg/m^3	
Idaho	Toxic air pollutants—pyrethrum		BNA 2001
	OEL	5 mg/m^3	
	EL	3.33x10^{-1} pounds/hour	
	AAC	0.25 mg/m^3	
Kentucky	Air quality—pyrethrum		BNA 2001
	TAL	20.0 mg/m^3	
	Averaging time	8 hours	
	Significant levels	1.276x10^{-3} pounds/hour	
Michigan	Air contaminant—maximum allowable concentrations		BNA 2001
	Pyrethrum	5 mg/m^3	
	Air contaminant (PEL-TWA)		BNA 2001
	Pyrethrum	5 mg/m^3	
Montana	Occupational air contaminant (TLV)		BNA 2001
	Pyrethrum	5 mg/m^3	
New Hampshire	Toxic air pollutants		BNA 2001
	Pyrethrum	5 mg/m^3	
New Mexico	Toxic air pollutants—pyrethrum		BNA 2001
	OEL	5.05 mg/m^3	
	Emissions	3.33x10^{-1} pounds/hour	

Table 8-1. Regulations and Guidelines Applicable to Pyrethrins and Pyrethroids *(continued)*

Agency	Description	Information	References
STATE *(cont.)*			
New York	Air contaminant (TLV)		BNA 2001
	Pyrethrum	5 mg/m^3	
Oregon	Air contaminant (TLV)	5 mg/m^3	BNA 2001
	Pyrethrum		
South Carolina	Toxic air emissions—pyrethrum		BNA 2001
	Maximum allowable concentration	50 μg/m^3	
Washington	Toxic air pollutants (ASIL 24-hour average)		BNA 2001
	Pyrethrum	1.7 μg/m^3	
Wisconsin	Emission limits—pyrethrum		BNA 2001
	<25 feet emission point	4.176x10^{-1} pounds/hour	
	>25 feet emission point	1.7520 pounds/hour	
b. Water			
Arizona	Drinking water guideline		HSDB 2001
	Fenvalerate	180 μg/L	
Florida	Drinking water guideline		HSDB 2001
	Permethrin	350 μg/L	
	Cypermethrin	700 μg/L	
c. Food		No data	
d. Other			
California	Pesticide registration—active ingredients		BNA 2001
	Fluvalinate		
	Permethrin		
	Pyrethrins		
	Resmethrin		
	Hazardous substance		BNA 2001
	Pyrethrins		
	Pyrethrum		
Florida	Toxic substances in the workplace—pyrethrum		BNA 2001

Table 8-1. Regulations and Guidelines Applicable to Pyrethrins and Pyrethroids *(continued)*

Agency	Description	Information	References
STATE *(cont.)*			
Georgia	Regulated substances and soil concentrations that trigger notification Pyrethrin I Pyrethrin II Pyrethrins and Pyrethroids Pyrethrum Pyrethrum I		BNA 2001
Massachusetts	Containers adequately labeled pursuant to federal law—pyrethrum		BNA 2001
	Oil and hazardous material Pyrethrin 1 Pyrethrin 2 Pyrethrins Pyrethroids Pyrethrum		BNA 2001
Minnesota	Hazardous substance—pyrethrum		BNA 2001
New Jersey	Hazardous substance Permethrin Phenothrin Pyrethrin I Pyrethrin II Pyrethrum Resmethrin Tetramethrin		BNA 2001

[a]Group 3: not classifiable as to its carcinogenicity to humans
[b]A4: not classifiable as a human carcinogen

AAC = acceptable ambient concentrations; ACGIH = American Conference of Governmental Industrial Hygienists; ASIL = acceptable source impact levels; CFR = Code of Federal Regulations; DOT = Department of Transportation; EL = emissions levels; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HAP = hazardous air pollutant; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; NIOSH = National Institute of Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; OEL = occupational exposure limit; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfD = oral reference dose; STEL = short-term exposure limit; TAL = threshold ambient limits; TLV = threshold limit value; TWA = time-weighted average; USDA = United States Department of Agriculture; WHO = World Health Organization

Table 8-2. Tolerances for Residues Applicable to Pyrethrins and Pyrethroids (ppm)

		Type I Pyrethroids		Type II Pyrethroids					
	Pyrethrin	Allethrin	Per-methrin	Cyper-methrin	Delta-methrin	Fenprop-athrin	Fenval-erate	Fluvali-nate	Tralo-methrin
	40CFR 180.128	40CFR 180.113	40CFR 180.378	40CFR 180.418	40CFR 180.435	40CFR 180.466	40CFR 180.379	40CFR 180.427	40CFR 180.422
Alfalfa, fresh	—	—	25.0	—	—	—	—	—	—
Alfalfa, hay	—	—	55.0	—	—	—	—	—	—
Almond hulls	—	—	0.05	—	—	—	15.0	—	—
Almonds	1.0	—	20.0	—	—	—	0.2	—	—
Apples	1.0	4.0	0.05	—	—	—	2.0	—	—
Artichokes	—	—	10.0	—	—	—	0.2	—	—
Asparagus	—	—	1.0	—	—	—	—	—	—
Avocados	—	—	1.0	—	—	—	—	—	—
Barley	3.0	2.0	—	—	—	—	—	—	—
Beans	1.0	—	—	—	—	—	—	—	—
Beans, dried	—	—	—	—	—	—	0.25	—	—
Beans, snap	—	—	—	—	—	—	2.0	—	—
Birdseed mixtures	3.0	—	—	—	—	—	—	—	—
Blackberries	1.0	4.0	—	—	—	—	—	—	—
Blueberries	1.0	4.0	—	—	—	—	3.0	—	—
Boysenberries	1.0	4.0	—	—	—	—	—	—	—
Brassica, head and stem	—	—	—	2.0	—	3.0	—	—	—
Brassica, leafy	—	—	—	14.0	—	—	—	—	—
Broccoli	—	—	1.0	—	—	—	2.0	—	0.5
Brussels sprouts	—	—	1.0	—	—	—	—	—	—
Buckwheat	3.0	—	—	—	—	—	—	—	—

Table 8-2. Tolerances for Residues Applicable to Pyrethrins and Pyrethroids (ppm) *(continued)*

		Type I Pyrethroids		Type II Pyrethroids					
	Pyrethrin	Allethrin	Per-methrin	Cyper-methrin	Delta-methrin	Fenprop-athrin	Fenval-erate	Fluvali-nate	Tralo-methrin
	40CFR 180.128	40CFR 180.113	40CFR 180.378	40CFR 180.418	40CFR 180.435	40CFR 180.466	40CFR 180.379	40CFR 180.427	40CFR 180.422
Cabbage	—	—	6.0	—	—	—	10.0	—	—
Cranberries	—	—	—	—	—	—	3.0	—	—
Cantaloupes	—	—	—	—	—	—	1.0	—	—
Carrots	—	—	—	—	—	—	0.5	—	—
Cattle, fat	0.1	—	3.0	0.05	—	1.0	1.5	0.01	—
Cattle, meat	0.1	—	0.25	0.05	—	0.1	1.5	0.01	—
Cattle, meat byproducts	0.1	—	2.0	0.05	—	0.1	1.5	0.01	—
Cauliflower	—	—	1.0	—	—	—	0.5	—	—
Celery	—	—	5.0	—	—	—	—	—	—
Cherries	1.0	4.0	3.0	—	—	—	—	—	—
Citrus, dried pulp	—	—	—	—	—	4.0	—	—	—
Citrus, oil	—	—	—	—	—	75.0	—	—	—
Cocoa beans	1.0	—	—	—	—	—	—	—	—
Coffee	—	—	—	—	—	—	—	0.01	—
Collards	—	—	20.0	—	—	—	10.0	—	—
Copra	1.0	—	—	—	—	—	—	—	—
Corn, fodder	—	—	60.0	—	—	—	50.0	—	—
Corn, forage	—	—	60.0	—	—	—	50.0	—	—
Corn, grain	—	2.0	0.05	—	—	—	0.02	—	—
Corn, including popcorn	3.0	—	—	—	—	—	—	—	—
Corn, sweet, kernels and cobs	—	—	0.1	—	—	—	0.1	—	—
Cottonseed	1.0	—	0.5	0.5	0.04	1.0	0.2	0.1	0.02

Table 8-2. Tolerances for Residues Applicable to Pyrethrins and Pyrethroids (ppm) *(continued)*

		Type I Pyrethroids		Type II Pyrethroids					
	Pyrethrin	Allethrin	Per-methrin	Cyper-methrin	Delta-methrin	Fenprop-athrin	Fenval-erate	Fluvali-nate	Tralo-methrin
	40CFR 180.128	40CFR 180.113	40CFR 180.378	40CFR 180.418	40CFR 180.435	40CFR 180.466	40CFR 180.379	40CFR 180.427	40CFR 180.422
Cottonseed, hulls	—	—	—	—	—	—	—	0.3	—
Cottonseed oil	—	—	—	—	0.2	3.0	—	1.0	0.2
Crabapples	1.0	4.0	—	—	—	—	—	—	—
Cucumbers	—	—	—	—	—	—	0.5	—	—
Currants	1.0	4.0	—	—	—	—	3.0	—	—
Dewberries	1.0	4.0	—	—	—	—	—	—	—
Eggplant	—	—	1.0	—	—	—	1.0	—	—
Eggs	0.1	—	1.0	—	—	0.05	—	0.01	—
Elderberries	—	—	—	—	—	—	3.0	—	—
English walnuts	—	—	—	—	—	—	0.2	—	—
Figs	1.0	4.0	—	—	—	—	—	—	—
Filberts	—	—	0.05	—	—	—	0.2	—	—
Flaxseed	1.0	—	—	—	—	—	—	—	—
Fruits, citrus, crop group 10	—	—	—	—	—	2.0	—	—	—
Fruits, pome, crop group 11	—	—	—	—	—	5.0	—	—	—
Garlic	—	—	0.1	—	—	—	—	—	—
Goats, fat	0.1	—	3.0	0.05	—	1.0	1.5	0.01	—
Goats, meat	0.1	—	0.25	0.05	—	0.1	1.5	0.01	—
Goats, meat byproducts	0.1	—	2.0	0.05	—	0.1	1.5	0.01	—
Gooseberries	1.0	4.0	—	—	—	—	3.0	—	—
Grain, sorghum	1.0	2.0	—	—	—	—	—	—	—
Grapes	—	4.0	—	—	—	5.0	—	—	—

Table 8-2. Tolerances for Residues Applicable to Pyrethrins and Pyrethroids (ppm) *(continued)*

		Type I Pyrethroids		Type II Pyrethroids					
	Pyrethrin	Allethrin	Per-methrin	Cyper-methrin	Delta-methrin	Fenprop-athrin	Fenval-erate	Fluvali-nate	Tralo-methrin
	40CFR 180.128	40CFR 180.113	40CFR 180.378	40CFR 180.418	40CFR 180.435	40CFR 180.466	40CFR 180.379	40CFR 180.427	40CFR 180.422
Grasses, range	—	—	15.0	—	—	—	—	—	—
Guavas	—	4.0	—	—	—	—	—	—	—
Hogs, fat	0.1	—	3.0	0.05	—	1.0	1.5	0.01	—
Hogs, meat	0.1	—	0.25	0.05	—	0.1	1.5	0.01	—
Hogs, meat byproducts	0.1	—	3.0	0.05	—	0.1	1.5	0.01	—
Honey	—	—	—	—	—	—	—	0.05	—
Honeydew melons	—	—	—	—	—	—	1.5	—	—
Horseradish	—	—	1.0	—	—	—	—	—	—
Horses, fat	0.1	—	3.0	0.05	—	1.0	1.5	0.01	—
Horses, meat	0.1	—	0.25	0.05	—	0.1	1.5	0.01	—
Horses, meat byproducts	0.1	—	2.0	0.05	—	0.1	1.5	0.01	—
Huckleberries	—	4.0	—	—	—	—	3.0	—	—
Kiwifruit	—	—	2.0	—	—	—	—	—	—
Leafy vegetables, except Brassica	—	—	20.0	—	—	—	—	—	—
Lettuce, head	—	—	20.0	10.0	—	—	—	—	1.0
Lettuce, leaf	—	—	—	—	—	—	—	—	3.0
Loganberries	1.0	4.0	—	—	—	—	—	—	—
Mangoes	1.0	4.0	—	—	—	—	—	—	—
Milk	—	—	—	0.05	—	—	0.3	0.01	—
Milk, fat	0.5	—	6.25	—	—	2.0	7.0	—	—
Milo	—	2.0	—	—	—	—	—	—	—
Mushrooms	—	—	6.0	—	—	—	—	—	—

Table 8-2. Tolerances for Residues Applicable to Pyrethrins and Pyrethroids (ppm) *(continued)*

		Type I Pyrethroids		Type II Pyrethroids					
	Pyrethrin	Allethrin	Per-methrin	Cyper-methrin	Delta-methrin	Fenprop-athrin	Fenval-erate	Fluvali-nate	Tralo-methrin
	40CFR 180.128	40CFR 180.113	40CFR 180.378	40CFR 180.418	40CFR 180.435	40CFR 180.466	40CFR 180.379	40CFR 180.427	40CFR 180.422
Muskmelons	1.0	4.0	—	—	—	—	1.0	—	—
Oats	1.0	2.0	—	—	—	—	—	—	—
Okra	—	—	—	—	—	—	0.1	—	—
Onion, bulb	—	—	0.1	0.10	—	—	—	—	—
Onions, green	—	—	—	6.0	—	—	—	—	—
Oranges	1.0	4.0	—	—	—	—	—	—	—
Papayas	—	—	1.0	—	—	—	—	—	—
Peaches	1.0	4.0	5.0	—	—	—	—	—	—
Peanut, hay	—	—	—	—	—	20.0	—	—	—
Peanut, nutmeat	—	—	—	—	—	0.01	—	—	—
Peanuts	—	—	—	—	—	—	0.02	—	—
Peanuts, with shell removed	1.0	—	—	—	—	—	—	—	—
Pears	1.0	4.0	3.0	—	—	—	2.0	—	—
Peas	1.0	—	—	—	—	—	1.0	—	—
Peas, dried	—	—	—	—	—	—	0.25	—	—
Pecans	—	—	—	0.05	—	—	0.2	—	—
Peppers	—	—	—	—	—	—	1.0	—	—
Peppers, bell	—	—	1.0	—	—	—	—	—	—
Pineapples	1.0	4.0	—	—	—	—	—	—	—
Pistachios	—	—	0.1	—	—	—	—	—	—
Plums	1.0	4.0	—	—	—	—	—	—	—
Potatoes	0.05	—	0.05	—	—	—	0.02	—	—
Poultry, fat	0.2	—	0.15	—	—	0.05	—	0.01	—

Table 8-2. Tolerances for Residues Applicable to Pyrethrins and Pyrethroids (ppm) *(continued)*

		Type I Pyrethroids		Type II Pyrethroids					
	Pyrethrin	Allethrin	Permethrin	Cypermethrin	Deltamethrin	Fenpropathrin	Fenvalerate	Fluvalinate	Tralomethrin
	40CFR 180.128	40CFR 180.113	40CFR 180.378	40CFR 180.418	40CFR 180.435	40CFR 180.466	40CFR 180.379	40CFR 180.427	40CFR 180.422
Poultry, meat	0.2	—	0.05	—	—	0.05	—	0.01	—
Poultry, meat byproducts	0.2	—	0.25	—	—	0.05	—	0.01	—
Pumpkins	—	—	—	—	—	—	1.0	—	—
Radish, roots	—	—	—	—	—	—	0.3	—	—
Radish, tops	—	—	—	—	—	—	8.0	—	—
Raisins	—	—	—	—	—	10.0	—	—	—
Raspberries	1.0	4.0	—	—	—	—	—	—	—
Rice	3.0	—	—	—	—	—	—	—	—
Rye	3.0	2.0	—	—	—	—	—	—	—
Sheep, fat	0.1	—	3.0	0.05	—	1.0	1.5	0.01	—
Sheep, meat	0.1	—	0.25	0.05	—	0.1	1.5	0.01	—
Sheep, meat byproducts	0.1	—	2.0	0.05	—	0.1	1.5	0.01	—
Soybeans	—	—	—	—	—	—	0.05	—	0.05
Soybean hulls	—	—	0.05	—	—	—	1.0	—	—
Spinach	—	—	20.0	—	—	—	—	—	—
Squash/cucumber subgroup	—	—	—	—	—	0.5	—	—	—
Stone fruits	—	—	—	—	—	—	10.0	—	—
Strawberry	—	—	—	—	—	2.0	—	—	—
Sugarcane	—	—	—	—	—	—	2.0	—	—
Summer squash	—	—	—	—	—	—	0.5	—	—
Sunflower seed	—	—	—	—	—	—	1.0	—	0.05
Sweet potatoes	0.05	—	—	—	—	—	—	—	—

Table 8-2. Tolerances for Residues Applicable to Pyrethrins and Pyrethroids (ppm) *(continued)*

		Type I Pyrethroids		Type II Pyrethroids					
	Pyrethrin	Allethrin	Per-methrin	Cyper-methrin	Delta-methrin	Fenprop-athrin	Fenval-erate	Fluvali-nate	Tralo-methrin
	40CFR 180.128	40CFR 180.113	40CFR 180.378	40CFR 180.418	40CFR 180.435	40CFR 180.466	40CFR 180.379	40CFR 180.427	40CFR 180.422
Tomatoes	1.0	4.0	2.0	—	0.2	0.6	1.0	—	—
Tomato (products) concentrated	—	—	—	—	0.1	—	—	—	—
Turnip greens	—	—	20.0	—	—	—	—	—	—
Turnip roots	—	—	1.0	—	—	—	0.5	—	—
Turnip tops	—	—	—	—	—	—	20.0	—	—
Vegetables, curcurbit	—	—	3.0	—	—	0.5	—	—	—
Walnuts	1.0	—	0.05	—	—	—	—	—	—
Watercress	—	—	5.0	—	—	—	—	—	—
Watermelons	—	—	—	—	—	—	1.0	—	—
Wheat	3.0	2.0	—	—	—	—	—	—	—
Winter squash	—	—	—	—	—	—	1.0	—	—

Source: EPA 2001f

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and μg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL-from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD_{50})—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A

ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Bioallethrin
CAS Number: 28434-00-6
Date: July 20, 2001
Profile Status: Third Draft Pre Public
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 14
Species: Mouse

Minimal Risk Level: 0.0007 [X] mg/kg/day [ ] ppm

Reference: Ahlbom J, Fredriksson A, Eriksson P. 1994. Neonatal exposure to a Type-I pyrethroid (bioallethrin) induces dose-response changes in brain muscarinic receptors and behaviour in neonatal and adult mice. Brain Res 645:318-324.

Experimental design and effects noted: The acute oral MRL is based on results of a study in which the most significant finding was the presence of altered motor behavior in adult mice treated with bioallethrin neonatally. Groups of 10-day-old male NMRI mice were treated by gavage with 0 (vehicle control), 0.21, 0.42, 0.7, or 42 mg bioallethrin/kg in a fat emulsion vehicle by gavage for 7 consecutive days (Ahlbom et al. 1994). At the age of 4 months, the mice were subjected to behavioral tests of spontaneous activity (locomotion, rearing, and total activity). Tests were conducted for 1 hour, and scores were summed for three 20-minute periods. Statistically significant increases in spontaneous activity of low-dose (0.21 mg/kg) mice, relative to controls, included increased locomotion during the last 20 minutes and increased rearing and total activity during the last 40 minutes. This was interpreted as a disruption of a simple, nonassociative learning process, (i.e., habituation), or a retardation in the adjustment to a new environment. The 0.42 and 0.7 mg/kg dose groups also exhibited significantly increased spontaneous activity, whereas significantly decreased spontaneous activity was observed in high-dose (42 mg/kg) mice. Receptor assays revealed a dose-dependent significant increase in muscarinic acetylcholine (MACh) receptor density in the cerebral cortex of 17-day-old mice given bioallethrin doses of up to 0.7 mg/kg/day, but a significant decrease in MACh receptor density in the cerebral cortex of those mice in the 0.21–0.7 mg/kg dose groups that were examined 1–2 weeks following behavioral testing at 4 months of age.

From this study, it is apparent that oral exposure of neonatal mice to bioallethrin levels below those resulting in overt signs of acute neurotoxicity may cause changes in receptor densities within the brain that can be observed shortly following treatment, and also following maturation. Neonatal exposure can also cause changes in behavioral patterns that are apparent in adulthood. However, a causal relationship between changes in the density of muscarinic cholinergic receptors in the cerebral cortex and increased spontaneous motor activity has not been established. The bioallethrin-induced increase in spontaneous motor activity at the dose of 0.21 mg/kg is considered a less serious LOAEL.

Dose and end point used for MRL derivation: 0.21 mg/kg; neurodevelopmental effects.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 3 for human variability

An uncertainty factor of 3 instead of 10 was used to account for human variability in the derivation of the MRL since the neonatal rat (10 days old) is a sensitive subject. In this experiment, bioallethrin was administered in a fat emulsion vehicle via gavage. No adjustment was made for effects of the fat vehicle on absorption because neonatal children are likely to be exposed to pyrethroids such as bioallethrin via breast milk that typically contains abundant fat.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure? No

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Deltamethrin
CAS Number: 52918-63-5
Date: July 20, 2001
Profile Status: Third Draft Pre Public
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 16
Species: Mouse

Minimal Risk Level: 0.002 [X] mg/kg/day [ ] ppm

Reference: Eriksson P, Fredriksson A. 1991. Neurotoxic effects of two different pyrethroids, bioallethrin and deltamethrin, on immature and adult mice: Changes in behavioral and muscarinic receptor variables. Toxicol Appl Pharmacol 108:78-85.

Experimental design and effects noted: The acute oral MRL is based on results of a study in which the most significant finding was the presence of altered motor behavior in adult mice treated with deltamethrin neonatally. Groups of 10-day-old male NMRI mice were treated by gavage with 0 (vehicle control) or 0.7 mg deltamethrin/kg in a fat emulsion vehicle by gavage for 7 consecutive days (Eriksson and Fredriksson 1991). Following treatment cessation, 17-day-old mice were tested for spontaneous activity (locomotion). At the age of 4 months, the mice were subjected to behavioral tests of spontaneous activity (locomotion, rearing, and total activity). Tests were conducted for 1 hour, and scores were summed for three 20-minute periods. Locomotor activity in the 17-day-old mice was not significantly different from that in controls. However, when tested at 4 months of age, deltamethrin-treated mice exhibited significantly increased locomotion and total activity during the last 20 minutes of the test period. This was interpreted as disruption of a simple, non-associative learning process, (i.e., habituation), or a retardation in adjustment to a new environment. Receptor assays, performed 1–2 weeks following behavioral testing at 4 months of age, revealed a significant trend toward a decrease in muscarinic acetylcholine (MACh) receptor density in the cerebral cortex of deltamethrin-treated mice. No significant treatment-related changes in this parameter were seen in two other brain regions, hippocampus and striatum.

From this study, it is apparent that oral exposure of neonatal mice to deltamethrin levels below those resulting in overt signs of acute neurotoxicity may cause changes in receptor densities within the brain that can be observed shortly following treatment, and also following maturation. Neonatal exposure can also cause changes in behavioral patterns that are first apparent in adulthood. However, a causal relationship between decreased density of muscarinic cholinergic receptors in the cerebral cortex and increased spontaneous motor activity has not been established. The deltamethrin-induced increase in spontaneous motor activity at the dose of 0.7 mg/kg is considered a less serious LOAEL.

Dose and end point used for MRL derivation: 0.7 mg/kg; neurodevelopmental effects.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 3 for human variability

An uncertainty factor of 3 instead of 10 was used to account for human variability in the derivation of the MRL since the neonatal rat (10 days old) is a sensitive subject. In this experiment, deltamethrin was administered in a fat emulsion vehicle via gavage. There was no adjustment made for effects of the fat vehicle on absorption because neonatal children are likely to be exposed to pyrethroids such as deltamethrin via breast milk that typically contains abundant fat.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Was a conversion used from intermittent to continuous exposure? No

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 9 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 6 **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

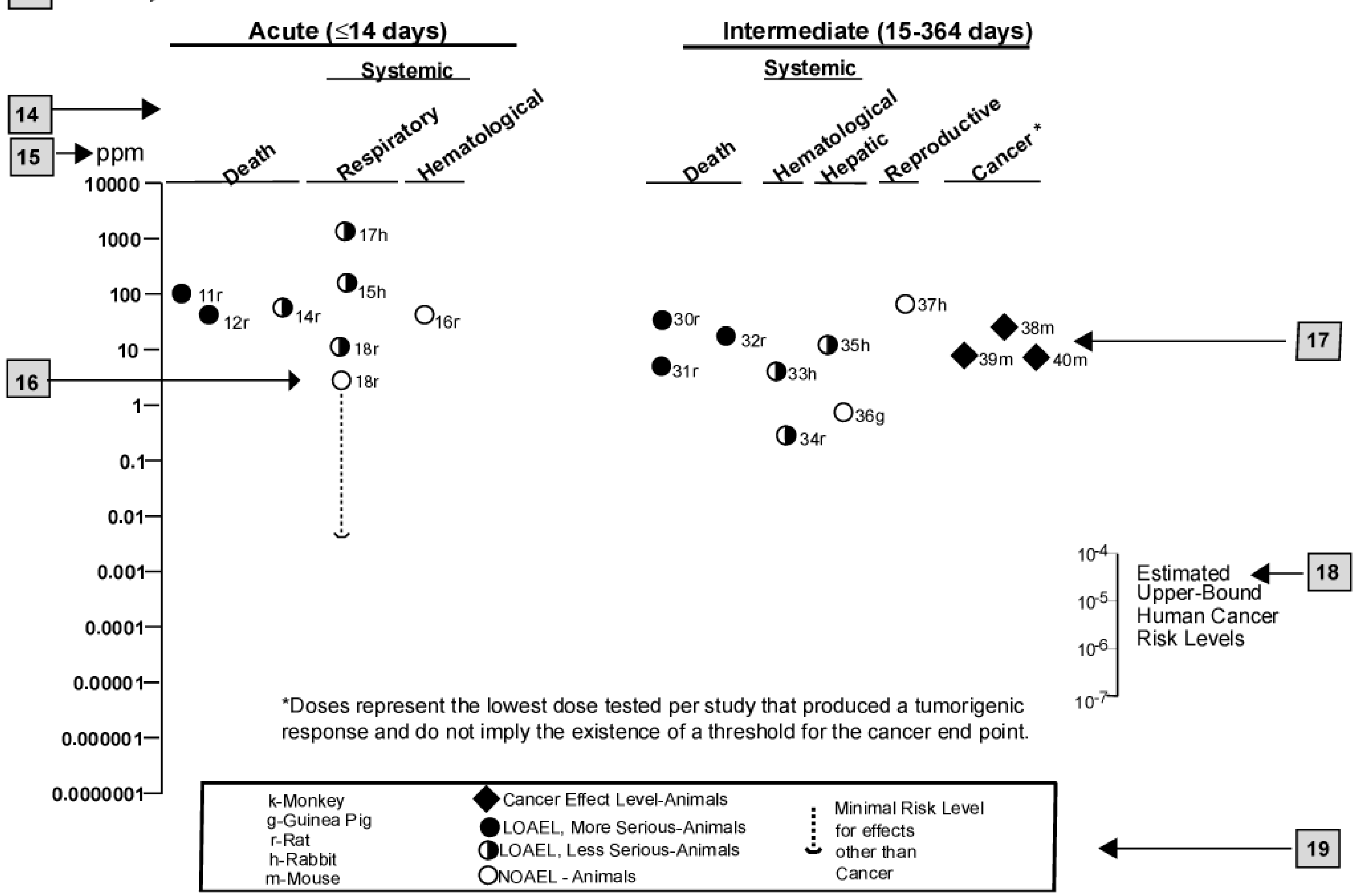
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 6 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 6 Systemic	9	9	9	9	9		9
4 6 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
						11	
Cancer						9	
38	Rat	18 mo 5 d/wk 7 hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 3-1.

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AVDI	Average Daily Intake
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
DCCA	cis-/trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/	Department of Transportation/United Nations/

APPENDIX C

DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPBA	4-fluoro-3-phenoxybenzoic acid
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MACh	muscarinic acetylcholine
MAL	Maximum Allowable Level

mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NA/IMCO	North America/International Maritime Dangerous Goods Code
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week
>	greater than
$\geq$	greater than or equal to
=	equal to
<	less than

≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D

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